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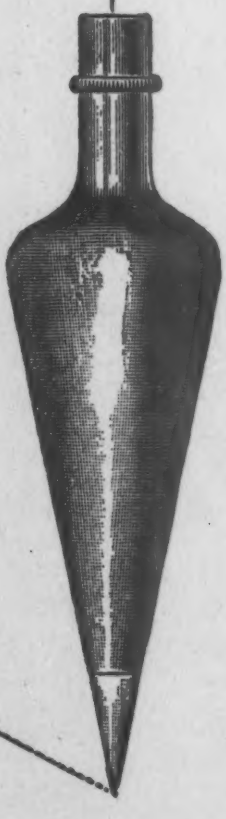

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ANNALS OF SURGERY

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INTRODUCTORY REMARKS—FIRST CHURCHILL LECTURE

Eldridge Campbell, M.D., Albany, New York

Dr. Churchill, Ladies and Gentlemen:

The fighting has ceased, the contending nations are licking their wounds and may now reckon their gains and losses. No country ever really wins in a war; one side simply loses more than the other. Medicine's part in the victory was bought at the price of serious dislocation both of graduate and undergraduate education.

Fortunately, there were valuable gains as well. Under the stimulus of war, far-reaching advances came in the fields of chemotherapy, preventive medicine, and above all in surgery. These were made possible by men whose devotion to their profession was such that they could serve their goddess despite the handicaps of personal discomfort, of makeshift temples, and of the petty annoyances of an *ersatz* officialdom which often appeared more interested in the stroma than the parenchyma.

Thus, it was but natural that a group of friends of long association in the Mediterranean Theater should found a lecture in honor of Doctor Churchill, whose devotion to surgery, as well as to those practicing it, whose wisdom and openmindedness made him the Paré of World War II. To this end we have secured the willing services of a distinguished American scientist, Dr. Alfred Blalock, Professor of Surgery at the Johns Hopkins Medical School, who will deliver the first Edward D. Churchill Lecture: Doctor Blalock.

THE USE OF SHUNT OR BY-PASS OPERATIONS IN THE TREATMENT OF CERTAIN CIRCULATORY DISORDERS, INCLUDING PORTAL HYPERTENSION AND PULMONIC STENOSIS*

Alfred Blalock, M.D.

Baltimore, Md.

FROM THE DEPARTMENT OF SURGERY OF THE JOHNS HOPKINS UNIVERSITY AND HOSPITAL, BALTIMORE, MD.

The surgeon with a profound interest in the physiopathology of disease is to a large extent a product of the period in which we are living. The man in whose honor this lectureship is named is one of the most ardent advocates of the physiologic approach to surgery. Dating from the time when he worked with Doctor Drinker, and others, Doctor Churchill has continued his own investigations and has fostered research among his associates and pupils. In addition, Doctor Churchill has shown an admirable combination of attributes as an excellent clinical surgeon, a great professor of surgery, a successful

* The first E. D. Churchill Lecture, delivered at Boston, Massachusetts, before the Excelsior Surgical Club, and Guests, October 25, 1946.

military surgical consultant, and a surgical philosopher. In this, the first Churchill lecture, it is with a feeling of gratification that I discuss certain abnormalities of the circulation in the solution of which the physiologic approach is proving useful. I wish that the subject were broad enough to embrace more of the interests of your honored member.

In the past, the major emphasis in surgery has been concentrated on the removal of diseased tissues or abnormal growths. Better means by which various structures may be removed will be developed, but the scope of surgery by extirpation cannot be extended greatly since the field has been covered rather completely. The operative procedures under consideration in this lecture are not concerned with extirpation but rather with improving the function of organs which are left *in situ*. It is to be hoped that the problems connected with the transplantation of tissues from one subject to another will be solved ultimately and that diseased organs may be replaced by normal ones. In the meantime, it appears that a good deal can be accomplished from the viewpoint of improving the function of structures that cannot be dispensed with or replaced.

Turning our attention more specifically to the circulatory system, we see how remarkably effective nature is in dealing with many of the congenital and acquired abnormalities. For example, survival is possible following occlusion of some of the larger arteries of the body provided the occlusion is gradual rather than sudden and that there is not generalized arterial disease. Owings[1] has demonstrated experimentally that it is possible to perform successful complete occlusion of the thoracic aorta in multiple-stage operations. Clinical case reports show that life is possible in the presence of complete closure of the three major coronary arteries or in congenital atresia of the thoracic aorta or main pulmonary artery. It has been demonstrated experimentally that the portal vein may be occluded by multiple-stage procedures without causing death, and that, in man, gradual closure of the portal vein may take place without a fatal result. The spontaneous development of large collateral pathways following the occlusion of arteries or veins is one of the best defense mechanisms of the body against disease and injury. Unfortunately, the collateral circulation is not always sufficient to maintain the life of the individual or the part. More often the part does not function normally even though death or gangrene does not occur. Under these circumstances, certain well-known surgical measures may be of aid. I refer in particular to the use of sympathectomy in various vascular disorders. Reference should also be made to attempts to increase the collateral blood supply to ischemic tissues by causing the part to adhere to neighboring structures, as in the Beck[2] procedure.

This lecture, however, will not deal with these measures but rather with those in which the course and function of large arteries or veins are altered in such manner that they will deliver blood to, or drain blood from, an area other than that which they previously served. The procedures represent an attempt to increase arterial circulation to areas or venous drainage from areas beyond that which is possible through the development of normally-occurring collateral

pathways. Major attention will be devoted to portal hypertension on the venous side and to pulmonic stenosis on the arterial side. In addition, a few of the other conditions in which the principle may be utilized will be discussed briefly.

Before beginning a consideration of individual disorders, a few general remarks concerning blood vessel anastomosis may be in order. Naturally, the most important point is that the anastomosis shall remain patent. This is dependent to a considerable extent upon the caliber of the vessels that are used and upon the expertness with which the anastomosis is performed. Also, of great importance is the difference in the pressures on the two sides of the anastomosis. Other factors being equal, those anastomoses are most apt to remain patent in which there is the greatest difference in pressure on the two sides of the union. If the pressures on the two sides are approximately the same, the vessel with a high pressure and a pulsating flow is more apt to remain patent than the one with a low pressure and a nonpulsating flow. The statement which I am about to make has not been confirmed by adequate experimental observations, but it is probable that an anastomosis of a systemic artery to a vein would be most likely to remain patent, that an anastomosis of a systemic artery to a pulmonary artery would rank next, that an anastomosis of an artery to another systemic artery would rank third, and that a vein-to-vein anastomosis would be least apt to remain open. As stated previously, other factors, including the caliber and length of the vessels, the site of the operation, and the care with which the anastomosis is performed, influence the incidence of thrombosis.

The question arises whether blood vessel anastomoses are performed best by suture methods or by nonsuture methods[3] in which material such as vitallium or tantalum is employed. Dr. T. N. P. Johns[4] and I found that a vein-to-vein anastomosis is more apt to remain patent when the suture method is used as compared with the nonsuture method employing the vitallium tube. This result would be expected, in view of the fact that it is preferable to leave as little foreign material as possible in the region of the anastomosis. When a gap has to be bridged it may be necessary to use some method other than direct suture, but this is not the procedure of choice under the usual circumstances.

A point in technic in the anastomosis of large arteries, such as the aorta, is concerned with the decision whether the suture should include the entire thickness of the wall of the vessel or whether one should attempt a so-called anatomic approximation of the different layers. This point was discussed recently by Doctor Crafoord and Doctor Gross[5] in relation to methods for uniting the ends of the aorta after the excision of a stenotic area. I agree with Doctor Gross that the suture should be an everting one and should include the entire thickness of the wall of the aorta. Further experimental work on this subject is needed. The problem does not arise in connection with the anastomosis of veins or of the smaller arteries in which the thin vessel wall will not permit an anatomic approximation of the different layers.

Another point which arises in connection with some of the operations is concerned with the performance of an end-to-end or an end-to-side or a side-to-

side anastomosis. In many cases only an end-to-end suture is feasible, but in others one of the other methods may be chosen. For example, in a splenorenal vein anastomosis one may unite the end of the splenic vein to the end of the renal vein after having removed the left kidney or may suture the end of the splenic vein to the side of the renal vein without doing a nephrectomy. Obviously, one advantage of the latter method is that the patient retains both kidneys. Some experimental work, which Doctor Johns[4] and I performed recently, indicates that there is an additional advantage to the end-to-side anastomosis, in that thrombosis is less likely to take place. It was found that 90 per cent of the splenorenal anastomoses remained patent when the end-to-side method was used, whereas only 73 per cent of the end-to-end anastomoses remained open. It is likely that the large venous return from the kidney aids in maintaining patency of the anastomosis in the end-to-side type. The problem arises in portacaval anastomoses whether one should suture the end of the divided portal vein to the side of the inferior vena cava or should perform a side-to-side suture. The latter method is more difficult to perform and the opening is less likely to remain patent. In the anastomosis of a systemic to a pulmonary artery which is to be discussed subsequently, the end-to-side union is preferable in that it allows the diverted arterial stream of blood to flow to both lungs. Thus, it is apparent that an end-to-side anastomosis is in some instances preferable to an end-to-end one.

Attention will now be directed to those abnormalities in which a by-pass or shunt operation should be considered. The first condition to be discussed is hypertension of the portal vein or its tributaries.

PORTAL HYPERTENSION

In a consideration of portal hypertension it should be remembered that the portal venous system is interposed between two capillary beds. The portal vein normally receives the venous drainage from the gastro-intestinal tract, the pancreas, the gallbladder, and the venous sinuses of the spleen. Patients with portal hypertension may be divided into those with intrahepatic block and those with extrahepatic block. Although it is not possible always to be sure as to the nature of the block, much information can be gained from certain observations. It is usually possible to predict, on the basis of studies of liver function, whether the hypertension is due to portal cirrhosis or to extrahepatic blockage of part, or all, of the portal bed. A patient with splenomegaly, bleeding from the intestinal tract, anemia, leukopenia, thrombocytopenia, and normal liver function tests most likely has extrahepatic portal bed block. A history of antecedent pancreatitis or severe trauma to the epigastrium suggests the possibility of thrombosis of the splenic vein. In the absence of a history of abdominal trauma, the young child with an enlarged spleen, repeated hematemeses, and normal liver function tests may have occlusion of the portal vein as a result of continuation of the obliterative process in the umbilical vein and ductus venosus. Abnormal liver function tests indicate an intrahepatic obstruction. Whipple[6] states: "If there is a high retention of bromsulphalein in the

blood 30 minutes after the intravenous injection, if the hippuric acid test is positive, if there is a reversal of the albumin-globulin ratio or if the cephalin flocculation test is positive, the presence of a cirrhosis with intrahepatic portal block is fairly certain. On the other hand, if these tests are negative it is safe to assume that the block is extrahepatic." It is obvious that patients with cirrhosis without portal hypertension do not fall within the scope of this lecture.

One of the difficulties in determining the site of extrahepatic blockage associated with hematemesis arises because of the variability in the point of entrance of the coronary veins. In some instances the coronary vein of the stomach enters the splenic vein, whereas in others it enters the portal vein. Rousselot[7] has shown that esophageal varices do not usually occur in the presence of thrombosis of the splenic vein when the coronary vein enters the portal vein. Under such circumstances, splenectomy in the treatment of congestive splenomegaly is indicated. On the other hand, if there are esophageal varices and splenic vein thrombosis and if the thrombosis is proximal to the entrance of the coronary vein, splenectomy should be performed only if a splenorenal vein anastomosis is performed at the same time. It is usually difficult to determine the site of extrahepatic venous thrombosis. Venous pressure readings and venograms give valuable aid. Blakemore and Lord[8] state that a venous pressure reading higher than 110 mm. of water should be considered abnormal. They advise the following course: "At the outset, a pressure reading should be taken from a branch of the superior mesenteric vein; if this is elevated, it may be taken as evidence of a block in the superior mesenteric vein, portal vein or intrahepatic portal block. A normal reading from a branch of the superior mesenteric vein and an elevated reading from a branch of the coronary vein of the stomach would indicate a block in the splenic vein, and, furthermore, strongly suggest that the coronary vein originates from the splenic vein distal to the site of obstruction. This evidence alone would make us favor performing a splenectomy followed by a splenorenal anastomosis rather than a splenectomy alone. In a case of congestive splenomegaly in which the superior mesenteric pressure is normal, the splenic vein pressure elevated but the coronary vein pressure approximately normal, we would be inclined to perform a splenectomy only." It is only fair to state that it is at times very difficult to determine accurately the venous pressure in these locations.

A difficult problem is presented by the patient with portal thrombosis and cavernomatous transformation of the portal vein. Under such circumstances the splenorenal vein anastomosis is probably the procedure of choice.

It is to be hoped that recent advances in the treatment of cirrhosis by the use of high protein-carbohydrate diet and high vitamin therapy will reduce the number of patients in whom some form of surgical therapy is considered necessary. On the other hand, it seems likely that many patients will develop portal hypertension and bleeding from the esophagogastro-intestinal tract. The problem of repeated bleeding is a particularly difficult one. My experience with the ligation of tributaries to esophageal varices has been very discouraging. The results of attempts to inject and coagulate varices leave much to be

desired, and the Talma-Morison omentopexy rarely results in improvement. The most physiologic method of surgical treatment is that in which an attempt is made to anastomose the portal and the caval circulations. The experience thus far with this method will be related briefly.

In 1877, Eck,[9] a Russian physiologist, developed the operation whereby a fistula between the portal vein and the inferior vena cava is made in order that he might carry out experimental studies of diseases of the liver and the relations of the liver to metabolism. He suggested that an anastomosis between the two veins might be used to sidetrack the venous return in obstruction of the portal vein. Quievolo,[10] in 1893, everted the divided distal end of the portal vein over a glass tube and connected this to an opening in the inferior vena cava. Some of the animals lived for a period of months. The Eck fistula procedure was attempted in patients by several surgeons in 1910, and shortly thereafter. Probably the most encouraging result was that of Rosenstein,[11] who created an Eck fistula in an elderly woman with cirrhosis. This patient was strikingly improved at the time of the report five months after the operation. The high mortality rate associated with the operation discouraged its use, and it is only recently that the employment of this procedure in patients has been revived.

The recent interest in portacaval shunts has resulted to a considerable extent from the nonsuture method for blood vessel anastomosis devised by Blakemore and Lord.[3] Whether or not one agrees with them that this method is preferable to a suture anastomosis, it is certain that it stimulated Whipple and Blakemore to the further use of the principle of the Eck fistula in the treatment of patients with intra- and extrahepatic block. At the time of their last report[12, 13] (February, 1946), 14 patients had been operated upon. In four of these patients the site of the portal bed obstruction was extrahepatic and in the remaining ten it was intrahepatic due to portal cirrhosis. A splenorenal vein anastomosis was performed in some of the cases and a portacaval shunt in others. There were only two early postoperative deaths, and the majority of the surviving patients were improved. When there is freedom of choice, Blakemore[13] is of the opinion that the portacaval shunt (anastomosis of divided distal end of the portal vein to the side of inferior vena cava) is preferable to the splenorenal anastomosis.

My own experience with this type of anastomosis is less extensive than that of Whipple and Blakemore, and the results are not so good as theirs. I think, however, that the procedure is a sound one. Because of the high portal pressure, the opening is more apt to remain patent than is the usual vein-to-vein anastomosis. There are several impressions which I have gained as a result of my experience: (1) Anastomosis of the portal vein and inferior vena cava is preferable when indicated to a splenorenal union in that it will conduct more blood and is more apt to remain patent; (2) if a splenorenal anastomosis is performed, suture of the proximal end of the splenic vein to the side of the renal vein is preferable to an end-to-end anastomosis; (3) suture of the divided distal end of the portal vein to the side of the inferior vena cava is preferable to

a side-to-side anastomosis since the opening is more apt to remain patent; and (4) it is not necessary to occlude the inferior vena cava completely while performing a portacaval shunt.

The foregoing remarks support the statement that portacaval shunt operations are still in the experimental stage and much remains to be learned about the choice of patients for operation and the choice of operative procedure. Despite the incompleteness of our knowledge, it does appear that the principle of portacaval shunts in the treatment of ascites and gastro-intestinal bleeding is a much sounder one than those previously advocated.

Before beginning a consideration of the treatment of pulmonic stenosis, I should like to mention briefly several other conditions in which the shunt, or by-pass operation, may be indicated.

MISCELLANEOUS CONDITIONS

The first to be considered is coarctation of the aorta. Doctor Park and I[14] showed experimentally that the transposed subclavian artery is capable of conducting sufficient blood to maintain life in animals in which the thoracic aorta is completely occluded. This method has been used in the treatment of only one patient* with coarctation because the method described by Crafoord,[15] and by Gross,[16] in which the stenotic area is excised and an end-to-end anastomosis performed, appears to be a better one. I believe, however, that there will be occasions when the use of the subclavian artery to by-pass the point of stenosis, or atresia, of the aorta will be indicated. For example, it may not be possible to perform excision and an anastomosis in the infantile type of coarctation in which the constricted zone is longer than in the adult type. In addition, the use of the subclavian artery as a by-pass may be advisable in the treatment of coarctation in adults in whom the aorta is diseased and inelastic.

The splenic artery may be used for conducting blood to the left kidney. Dr. Richard Kieffer and I[17] showed experimentally that when the divided proximal end of the splenic artery has been connected to the distal end of the divided left renal artery there has been no evidence of renal failure even though the right kidney is removed. It is unlikely that this particular method will have clinical significance since disease limited to the first part of the renal artery is very rare. Another possible use of the splenic artery is as a replacement for the first part of the superior mesenteric artery.

Dr. William Longmire[18] has recently anastomosed the internal mammary vessels to the mesenteric vessels of a segment of jejunum which he was employing in the creation of an artificial esophagus. Easily palpable pulsations could be felt beyond the point of the anastomosis. Even though the lumen of the mammary vessels should subsequently become occluded, the procedure should prove helpful in maintaining viability of the intestine in the early critical

* This patient, unfortunately, has a partial paralysis of the lower extremities. In a recent personal communication, Dr. O. T. Clagett, of the Mayo Clinic, describes a brilliant result following the anastomosis of the subclavian artery to the aorta distal to the point of stenosis.

period before additional collateral pathways have had time to become enlarged.

In the treatment of an aneurysm of the first part of the common carotid artery in which the compression test indicates that ligation of the artery will not be tolerated, one might substitute the adjacent subclavian artery for the carotid. Ligation of the first portion of the subclavian is associated with little risk. There is not a great deal of difference in the caliber of the common carotid and subclavian arteries and an anastomosis is feasible.

Additional knowledge concerning the functions of the liver may make it advisable under certain circumstances to reroute the venous return from one or more of the abdominal organs in such a manner that the blood will return to the heart without passing through the liver. For example, it is possible, but not likely, that benefit would result from having the pancreatic venous return reach the heart without traversing the liver. Even if such were the case, however, the technical difficulties would be considerable.

It is unlikely that the reverse of the procedure which is used in the treatment of pulmonic stenosis can be used in the treatment of aortic stenosis. The success of the operation for pulmonic stenosis is dependent upon the higher pressure on the aortic side which causes blood to flow to the lungs. Even in the presence of severe aortic stenosis, the blood would probably flow from the systemic to the pulmonary system and the patient would not be helped.

The excellent course of most of the patients with the "tetralogy of Fallot" in whom an artificial ductus arteriosus has been established has made me wonder whether the associated interventricular defect does not serve as a safety valve in preventing heart failure. If this be true, the question arises whether induced interventricular and interauricular defects may not be helpful in the treatment of other cardiovascular abnormalities. Levine has aptly remarked that an automobile runs better with two flat tires than with one, and it may very well be that a balancing of the two sides of the heart may be desirable in the presence of certain unilateral abnormalities. In other words, the creation of an interauricular or an interventricular defect which will allow the blood to flow from a chamber with high pressure to one with a lower pressure may under certain circumstances be of an advantage.

A number of the ideas put forth in this section dealing with miscellaneous conditions are based upon theory and have not been put to practical test. Such is fortunately not true to the same extent in pulmonic stenosis, the subject to which we will now turn.

PULMONIC STENOSIS OR ATRESIA

The most frequently encountered type of congenital cardiovascular defect accompanied by cyanosis is the "tetralogy of Fallot," which is characterized by pulmonic stenosis or atresia, interventricular septal defect, dextroposition of the aorta, and right ventricular hypertrophy. Prior to the initiation of the work by Doctor Taussig and myself,[19] only one attempt had been made by operative means to increase the circulation to the lungs in the treatment of pulmonic stenosis. The operation performed by Doyen,[20] in 1913, consisted

of an attempt to divide what was believed to be a stenotic valve with a tenotome knife. The patient died several hours later, and examination revealed the usual finding of narrowing of the conus rather than stenosis of the valve. It is only necessary to examine an autopsy specimen of a stenosis of the conus to realize that division of this area would not only be dangerous but would very likely not result in permanent improvement. The stenosis would probably recur even if the area were excised.

It is rather strange that previous attempts to improve the condition of patients with the "tetralogy of Fallot" by the construction of an artificial ductus had not been made. The fact that the volume of the pulmonary blood flow is greatly decreased must have been recognized. The realization that there were associated abnormalities such as the interventricular defect and the overriding aorta probably caused doubt as to the value to be derived from an operation. Furthermore, it was probably not realized that one of the branches of the arch of the aorta can usually be connected to a pulmonary artery without great difficulty. In the beginning we were somewhat skeptical as to the benefit that might be derived from the making of an artificial ductus, but the results of experiments encouraged us to proceed. Even then, I was fearful that cyanotic children would not withstand anesthetization and temporary occlusion of one of the two pulmonary arteries. Furthermore, it was feared that the use of the subclavian artery would result in ischemia of the arm. Experience[21] has shown that our apprehension was in the main unwarranted—most of the children survive the operative procedure, and the collateral circulation to the arm is adequate.

The underlying principle in the choice of patients for operation is that there be inadequate flow of blood to the lungs. The history and the results of physical examination are of some aid. The two outstanding diagnostic features are roentgenographic evidence that the pulmonary artery is small in size and clinical and roentgenographic evidence of absence of congestion in the lung fields. Doctor Taussig and her associates have shown remarkable skill in diagnosing the condition correctly. Additional help has been supplied in recent months by Dr. Richard Bing, who has developed methods by which the blood flow through the pulmonary arteries, the total pulmonary blood flow including that through collateral channels, and the systemic blood flow can be determined with a fair degree of accuracy. These new tests have been of great aid in arriving at a correct decision in doubtful cases. Another diagnostic method which should be available and which we have not used to the desired extent is that of visualization of the heart and great vessels after the injection of radiopaque substances. The technics are available and the method should be employed.

It is now possible to predict with a fair degree of accuracy the danger associated with the operation in individual patients. In patients between the ages of two and twelve years in whom there is a typical "tetralogy" with a small heart, the mortality rate should be less than 12 per cent. When, however, atypical conditions such as a large heart, a large aorta, rotation of the heart,

situs inversus, or left axis deviation are present, the danger associated with the operation increases considerably.

The ages of patients who have been operated upon have ranged from four months to 26 years. The age preferred is from three to ten years. The operation is accompanied by a higher mortality rate in infants under two years of age. Operation is not advised in those 18 months and younger, unless the child is doing very poorly and it appears that the chances of survival to an older age are less than 50 per cent. The operation is usually more difficult from a technical standpoint in patients who have attained most of their growth. This is due to the fact that the gap to be bridged by the subclavian artery is greater in proportion to the length of the artery. Furthermore, the structures do not seem to be as elastic and pliable as in younger subjects.

There has been no recent change in our ideas as to the type of anastomosis or the choice of systemic vessel. An end-to-side anastomosis—that is, the union of the end of the systemic artery to the side of one of the two pulmonary arteries—is much to be preferred to an end-to-end union. The end-to-side anastomosis not only allows the blood to flow to both lungs but it exposes the patient to less risk of the development of pulmonary edema and heart failure. Furthermore, the end-to-side anastomosis does not preclude the possibility of a similar operation being performed on the opposite side at a later date.

In most patients who are more than two years of age the subclavian artery is the vessel of choice. The use of this vessel decreases greatly the danger of cerebral difficulty which may be associated with ligation of the innominate or carotid artery. In addition, there is less danger of heart failure as a result of the establishment of the fistula. Using the figures for arterial oxygen saturation reported by Doctor Taussig and myself, Dr. C. S. Burwell[22] has shown that additional elevations of arterial oxygen saturation after a rise from a low level to 75 to 80 per cent is attained may be reached at considerable expense in terms of cardiac strain. The arterial saturation in patients with the "tetralogy of Fallot" will never reach the normal level of 96 per cent, regardless of the caliber of the artery used, because of the admixture of venous and arterial blood as a result of the septal defect. The desired aim is to use a systemic artery which is of such a caliber that the polycythemia and cyanosis will disappear but which is not large enough to place undue strain on the heart. The subclavian artery seems to be large enough in most patients more than two years of age. This statement should be qualified by saying that the size of the fistula may prove to be inadequate in some of these children as they increase in size. If so, the operation can be repeated on the opposite side. It has not yet been determined whether the fistula will increase in size with the growth of the patient. At any rate, it appears at the present time that the subclavian artery should be used when its caliber indicates that it will conduct sufficient blood to the lungs to cause a disappearance of the polycythemia and cyanosis; otherwise the innominate or carotid artery should be chosen.

In patients under 15 years of age the incision in the chest is usually made on the side opposite to that on which the aorta descends. In approximately one

patient in five the aorta descends on the right rather than the left. The innominate artery arises on the side opposite to that on which the aorta descends. It is desirable to use the subclavian branch of the innominate rather than the opposite subclavian which arises directly from the aorta since the former vessel makes a less acute angle with its parent artery after the anastomosis is performed.[23] Furthermore, exposure of the innominate allows one to use this artery or its carotid branch if the subclavian artery is too small or too short. In older patients with long chests, there may be difficulty in approximating the subclavian artery to the pulmonary. For this reason, at times we utilize the subclavian branch of the aorta in the older age-group even though the resulting angulation is not desirable.

Probably the most frequent error that will be made in the performance of this operation will consist in mistaking the pulmonary artery to the right upper lobe for the main right pulmonary artery. In approximately one patient in five, the main right pulmonary artery divides early. The branch to the middle and lower lobes may arise in the mediastinum at the pericardial reflection. Unless one realizes this fact, one may perform, or attempt to perform, an anastomosis between the systemic artery and the pulmonary artery to the upper lobe. This is usually unsatisfactory because of the small caliber of the latter vessel. Unless the major branches to the right lung can be identified, one should persist in the dissection until the pericardial attachments have been freed and almost the entire length of the right pulmonary artery has been exposed. In this discussion the right side has been emphasized because early branching of the left pulmonary artery appears to occur less frequently. It should be added that the dissection is difficult if there are dilated collateral arterial pathways.

Difficulty may arise in identifying the pulmonary artery of one of the lungs and in distinguishing it from a pulmonary vein. This is particularly apt to occur if the pulmonary artery is diminutive in size and in an abnormal location. Furthermore, it is well to remember that the pulmonary artery may be absent. The position and course of the vessel and the pressure within the vessel are of aid in identification.

A sterile apparatus with which the pressure in the pulmonary artery may be measured is available at all our operations. This consists of a syringe and needle which are connected to a water manometer. If the pulsations in the pulmonary artery are not easily visible, the pressure is not measured. If the pulsations are strong, thereby casting doubt on the correctness of the diagnosis of pulmonic stenosis, the pressure is measured. In the great majority of our patients the pressure has been under 240 mm. of water and the anastomosis has been performed. If the pressure is well in excess of this figure, there is a strong likelihood that the diagnosis is in error. It is important to emphasize that the caliber of the pulmonary artery is not a good index of the pressure within the vessel. The pressure in several of the largest pulmonary arteries has been quite low.

As I stated previously, an end-to-side anastomosis is much to be preferred

to an end-to-end one. When the systemic artery is short, there may be considerable difficulty in performing the operation. If the anastomosis can be carried out by the use of fine suture material, the tension in the postoperative period will not be too great to prevent healing. After the instruments are removed and the lung is reinflated, the tension on the suture line appears to diminish. There has been no instance in which the vessels have separated. The most important points in technic are placing the sutures in such fashion that the intima is everted and adventitia is not pulled between the intimal surfaces, and taking care that the sutures are not pulled too tightly.

The average time required for the operation has been approximately two hours. In the majority of cases, no great haste is necessary. In the occasional patient, however, occlusion of one of the pulmonary arteries is tolerated poorly and the more quickly the anastomosis is performed the better.

My associates and I have now operated upon 243 patients who were thought to have the "tetralogy of Fallot." The over-all mortality rate, including deaths among those in whom an anastomosis could not be performed, those in whom the diagnosis was in error, and those who have died since leaving the hospital, has been 21 per cent. The mortality rate in the second 100 patients was 15 per cent. In the patients (approximately 147) in whom an anastomosis between the end of a subclavian artery and the side of the pulmonary artery was performed the mortality rate was 9 per cent. On the other hand, the mortality rate among those in whom the carotid or innominate artery was used (approximately 57) was 33 per cent. It is only fair to state that the long waiting list of patients has more or less forced us to choose for early operation those patients who are doing rather poorly and for whom postponement of operation would be a serious risk. Even so, 20 or more patients have died while awaiting admission to the hospital.

The follow-up periods are still of too short duration to allow evaluation of the final results. It can be stated that many of the children appear to be normal, that cardiac enlargement after the first several weeks is not progressive, and that, thus far, *Streptococcus viridans* infection has not developed. There have been no instances of empyema or mediastinitis.

SUMMARY

The purpose of this lecture has been to discuss certain abnormalities of the circulatory system in which treatment by shunt or by-pass operations is proving effective or may be found to be useful. Particular emphasis has been placed on the treatment of portal hypertension and pulmonic stenosis. It is hoped that the advances thus far recorded will serve as an added stimulus for further studies in which efforts will be made to improve the arterial in-flow or the venous return of important organs.

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THORACIC SURGERY IN A HOSPITAL CENTER

Col. Laurence Miscall, M.C.,
and
Major Albert W. Harrison, M.C.

Part I

The data from the records of 300 patients treated for thoracic battle injuries since D-day in the 804th Hospital Center, supplies the material for this report. It will be presented under three broad aspects:

(A) A review of the situation before admission to the Thoracic Center.

(B) A report of activities in the Thoracic Center.

(C) Recommendations for the care of thoracic casualties.

A—SITUATION BEFORE ADMISSION TO THE THORACIC CENTER

Records.—Many records have lacked final diagnosis, operative findings and procedure, details of specific treatment and laboratory and roentgenologic reports. This has precluded uniform comparative statistical study and provided frequently an uncertain basis for continuation of therapy.

First-aid and Emergency Care.—Treatment at all forward echelons has been reduced to essentials. The necessity for prompt control of hemorrhage, immediate restitution of cardiorespiratory function and prevention of infection have been fully appreciated. Packing and occlusive dressing of sucking wounds, positioning, sedation and early chemotherapy have been effectively used on the field. Treatment has progressed through ensuing stations. Plasma has been used freely in shock. A few sutures or ligatures have improved hemostasis and wound closure. Hemothorax and tension pneumothorax have been recognized and relieved by aspiration as indicated. After these simple measures, excellent judgment has governed priority of evacuation. Medical personnel should realize that these conservative measures have preserved many patients for subsequent care and cure in hospitals.

Field and Evacuation Hospitals.—At the Field and Evacuation hospitals, diagnostic aids and surgery have been judiciously employed in spite of many difficulties.

Shock.—Shock therapy has been necessarily continued in the majority of cases. As much as 3,500 cc. of blood and plasma have been given in 24 hours, usually with life-saving results. When the accentuation of shock by hemothorax, tension, cardiac injury and anoxia has been occasionally overlooked, large infusions of any type have precipitated serious episodes. Occlusion of wounds, pleural and bronchial aspiration, oxygen and replacement of blood loss have generally sufficed either to cure or carry the patient to operation in optimum condition. In some extensive injuries emergency surgery has been imperative to control shock and has given many results which must be considered excellent in such grave situations.

Wounds.—After recovery from shock, or when otherwise indicated, wounds have been well-attended. The relative constancy in each type deserves some mention for the aid it may lend in the future.

Tangential nonpenetrating wounds associated with thoracic damage necessitating evacuation to the Center have not been common. Severe atelectasis has been seen more often than extensive hemorrhagic consolidation. It has yielded to clearing of the air-ways. Hemorrhagic pneumonitis, except the massive type, had generally cleared without treatment before admission to the Center. Both have been confused with fluid and nonproductive aspiration repeated in spite of rather typical signs, symptoms and roentgenograms. Hemothorax has often followed but has required frequent tapping only when atelectasis or other factors caused persistence. These wounds have presented few thoracic problems.

Rifle bullets have often pierced the thorax without immediately serious consequences. Small nonsucking wounds, minimal hemothorax and lack of pulmonary collapse have been noted frequently. Direct tracts have been visualized on early roentgenograms as a hole through lung with circumferential clouding, presumably hemorrhagic pneumonitis, which has not exceeded a lobar distribution. Some with normal primary films have soon exhibited a massive atelectasis, of which concussion and retention of bronchial exudate have been prominent antecedents. Pneumonitis, atelectasis and other findings have cleared as early as seven days after injury, with complete healing in four weeks. Most have recovered without admission to the Center with initial dressing, bronchoscopy, chemotherapy, sedation, rest and occasional thoracentesis. Suppuration has not been common in the few requiring further treatment.

Shell fragments have produced fairly typical patterns. Small ones with little inertia have produced small nonsucking wounds, minor lung trauma and limited hemothorax or hemopneumothorax. With rapid sealing of visceral pleura retention of them has been frequently asymptomatic and not always injurious. Early recovery with conservatism has been quite uniform. Few have required secondary surgery except for extraction of the fragments. Large missiles have usually had a different course due to their size, ragged shape and motion. Open or sucking wounds, major loss of tissue, marked hemothorax, tension and imbedding of foreign material have been common. Such wounds usually have required débridement and intuitive plastic closure. Severe clinical condition has persisted until admission to a hospital, in spite of prompt first-aid. Resources have been taxed to supply the necessarily intensive therapy of shock, hemorrhage and tension so common in these patients.

Hemothorax and Hemopneumothorax. — Hemothorax or hemopneumothorax have been rather constant. They have responded usually to aspiration and penicillin. Primary closed drainage has been necessary often because marked hemopneumothorax and tension have repeatedly recurred after extensive trauma. In these difficult cases it has been superior to repeated aspiration or the flutter-valve. Some poor results have occurred because such primary drainage has not been used to meet these adverse conditions.

Exploratory Thoracotomy.—When conservative measures have not

promptly restored and adequately maintained cardiorespiratory function, surgical approach to the problem has been imperative. Results have been impressive. Intrathoracic procedure has been principally concerned with control of hemorrhage, repair of lacerations of the lung, diaphragm and viscera and removal of some large foreign bodies. Patients *in extremis* have bounded back because of surgical reëstablishment of circulation and respiration. Half-measures have given way to definitive surgery when the problem has been clearly appraised and skilfully managed.

The excellence of some results warrants brief comment on the mistakes. Pentothal or local anesthesia have been utilized to avoid the more time-consuming administration of a general anesthetic with endotracheal technic. The inability to control respiration has prevented or prematurely terminated some advisable operations. Continuing hemorrhage has not been promptly recognized and controlled. Inattention to the flooding of the air-ways has predisposed to atelectasis. Unnecessary sacrifice of ribs and soft tissues has promoted chest wall flaccidity, embarrassed respiration and complicated subsequent course and treatment. Late complications have been closely related to the retention of foreign bodies, inadequate closure of lacerations of the lung or diaphragm and insufficient drainage.

Chemotherapy.—Local and systemic sulfa-therapy has been started, almost without exception, on the field soon after injury. Irregularly in the hospitals it has been continued and supplemented or displaced by the administration of penicillin. More carefully controlled records are essential before the exact benefit of each agent can be more than an impression.

Evacuation.—With few exceptions, patients have arrived at the U.K. Base Hospitals in excellent condition. The early medical care, holding of patients and air evacuation, which has not been hazardous, have been largely responsible for this. With slow evacuation by train and repeated hospitalization, continuity of medical supervision has been lost. Lack of treatment in transit has predisposed to an increase in the number and the complexity of secondary operations, with a corresponding reduction in the ability to return to duty. When evacuation has been slow, intensive conservative therapy has been extremely valuable in situations not always subject to prompt improvement. Rapid evacuation has distinct military value in the increased numbers of wounded who return to duty because they either avoid surgery or receive it before chronicity demands major procedures and long convalescence.

General Hospitals (U. K.).—Despite all forward efforts hemothorax and hemopneumothorax have been the commonest initial problems at the General Hospitals. By aspiration the pleural space has been maintained as dry as possible. As much as 1,200 cc. of blood and air have been removed at one time. Any one aspiration has been discontinued at the onset of disturbing dyspnea, cyanosis, cough, tightness, tachycardia, or shock. After each aspiration 40,000 units of penicillin in 10 cc. of saline have been instilled. Table I details the data available on 100 patients clearing with this therapy. Sixty-nine cases without primary drainage cleared completely on five taps during which an

average maximum total of 2,900 cc. was removed. Thinning to serous quality, progressive clearing of roentgenograms and clinical improvement have been the best guides in treatment. Twenty-four other patients in whom more serious injury was treated by primary closed drainage recovered with subsequent treatment as shown on Table I. It is significant that 15 of these cases required

TABLE I

DETAILS OF ASPIRATION AND CHEMOTHERAPY IN 100 CASES NOT REQUIRING SECONDARY OPERATION AT THE THORACIC CENTER

NO PRIMARY DRAINAGE

No. Aspirations at Center	No. of Cases	Avg. Total Removed. Cc.	Adequate Chemotherapy	Inadequate Chemotherapy
1	5	0	..	..
1	13	375	8	4
2	18	1,000	7	2
3	18	1,100	9	1
4	6	1,600	2	2
5	9	2,900	5	1
	69		31	10

PRIMARY DRAINAGE

No. Aspirations Postoper.	No. of Cases	Avg. Total Removed Cc.	Adequate Chemotherapy	Inadequate Chemotherapy
0	15	0	5	4
1	0	0	0	0
2	6	700	3	1
3	0	0	0	0
4	0	0	0	0
5	3	2,200	2	0
	24		10	5

no subsequent aspiration and six were cured with two aspirations. In three cases needing five or more aspirations, the drainage tube had been removed in less than 48 hours, which appeared insufficient for stabilization of the pleura.

Chemotherapy, particularly intrapleural penicillin, probably has contributed to recovery without suppuration in this group since the fluid was definitely contaminated in ten cases. Yet this success cannot be resolved solely in its favor. The resistance of the pleura to infection, correction of anatomic defects, removal of the culture medium and obliteration of the pleural space by prompt lung expansion may have been underestimated. The complete recovery of 15 patients (Table I), whose records indicate totally inadequate chemotherapy, supports the contention that these factors are of great importance.

In a survey of 500 admissions to all hospitals, 70 per cent of hemothoraces have been observed to clear all chest symptoms, signs and roentgenograms in four to six weeks with such conservative therapy. Close scrutiny did not reveal any thoracic contraindication to early return to full duty. Medical officers have not been always quick in recognizing the necessity of surgery with the failure of these measures. Continuation of ineffective methods has allowed frequent progression to chronicity before transfer to a Thoracic Center.

B—ACTIVITIES AT THE THORACIC CENTER

The concentration of the resistant cases in Centers has yielded many observations upon which the efficiency of present methods may be partially evaluated. Although the transient follow-up, lack of comparative control series and other factors, prohibit sound deductions in many specific problems, significant facts deserve consideration as tentative guides for the future.

All patients have been admitted to the Thoracic Center for treatment of sequelae which can be broadly classified as follows:

1. Persistent hemothorax or hemopneumothorax. The fact that they have been clotted and unclotted; contaminated and uncontaminated; suppurative and nonsuppurative with and without underlying pathologic findings has added to the complexity of the problem.
2. Abdominothoracic injuries.
3. Retained foreign bodies.

Persistent Hemothorax and Hemopneumothorax. — In considering this problem it is important to ascertain why and when they are persisting before any logical step in diagnosis and treatment can be taken. In this survey these factors have been found to predispose to such persistence or recurrence.

1. Inadequate aspiration has often resulted from difficulties introduced by the military situation, associated injuries, evacuation and other events. Circumvention of these has received resourceful attention which has not always succeeded. The failure to aspirate small amounts has been an error. They have concealed foreign bodies, clotted, and become infected often. Nonremoval of air in the presence of blood has promoted multiple loculation, with subsequent inability to clear the pleural space by aspiration and expand the lung. This has been followed frequently by infection.

2. Atelectasis has been frequently overlooked. The early appearance of dyspnea, cough, physical signs and ground-glass roentgenograms with elevated diaphragm and retraction to the affected side with a previous history of pulmonary concussion, bloody or mucoid sputum, tangential or open-wounding, operation and shock have been typical. Symptoms and rapid reaccumulation after moderate aspiration (500 cc.) have repeatedly indicated its presence. Instillation of air to relieve symptoms has caused multiple loculation. Pleural fluid and atelectasis have subsided following bronchoscopic relief as late as 21 days after trauma.

3. With metallic foreign bodies in or communicating with the pleural space, fluid has persisted, recurred or become infected. Even small bodies near subpleural vessels have caused late serious hemorrhage. Chemotherapy has enhanced results when removal has been unavoidably delayed.

4. Residual defects have been prominent offenders. Bronchopleural fistulae have been almost universally associated with recurrent hemopneumothorax. Although brisk hemorrhage from lung has been rare, parenchymal tracts have continued to weep. Subpleural abscesses have often stimulated effusion and by rupture have produced empyema. Such defects have not been corrected by exploration, as indicated by the routinely poor reaction to primary treatment.

5. The neglect and misuse of closed drainage have led to much reaccumulation, which has often exceeded the range of applicability of aspiration. When it has been discontinued before stabilization and subsidence of pleural secretion, multiple loculation and infection have been usual.

6. Abdominothoracic wounds which deserve separate comment complete the list of common causes.

Information denoting abnormal persistence and the activity of these factors has been available but not carefully regarded. The figures from 72 operative cases are illustrative. In 47 of them aspiration in excess of five taps of 2,900 cc. was not accompanied by the usual signs of improvement. In the other 25, clotting prevented withdrawal of fluid. Ineffective aspiration was continued and progress for which surgery offered the only solution was not recognized in many until suppuration had resulted.

The futility of continuing conservatism under such circumstances may be clarified after a review of the pertinent facts. Blood in a chest compresses lung and will clot in time. A tough, inelastic, fibrohemorrhagic membrane organizing on the parietal and visceral pleura immobilizes lung, chest wall and diaphragm. It soon becomes difficult to separate. Since the chief surgical implication has been the membrane rather than the clot, "constrictive pleuritis" has seemed a better term than "clotted hemothorax." Reduced breathing capacity of fused chests makes pulmonary cripples of such patients. In a surprisingly short time (two to four weeks) the membrane has become so inelastic that neither aspiration nor drainage permit the lung to expand properly. Nothing short of removal of the membrane, decortication, has sufficed. If this has been delayed too long, infection has often supervened. Suppuration in the clot encased by the membrane has given empyemata that are chronic at inception. Bronchopleural fistulae, foreign bodies and pulmonary suppuration have been prominently associated with such developments. Chemotherapy has played a

TABLE II

THORACIC DISTRIBUTION OF 200 CONSECUTIVE OPERATED PATIENTS

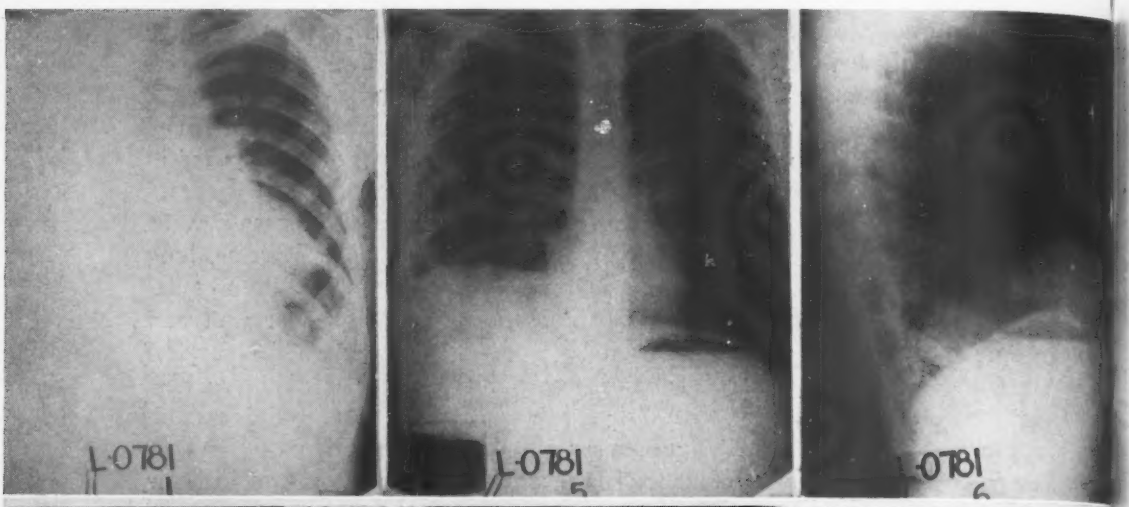
804th Hospital Center—U. S. Army

Diagnosis	Number	% Total
1. Empyema, acute	14	7.0
2. Constrictive pleuritis (clotted chest, simple)	29	14.5
3. Constrictive pleuritis (suppurative)	39	19.5
4. Abdominothoracic injuries	28	14.0
5. Foreign bodies	98	49.0
(elective removal):		
a. Heart and great vessels	20	
b. Mediastinum	10	
c. Lung and pleura	68	
6. Foreign bodies	40	
(incidental removal):		
a. Pleura	15	
b. Lung	25	
Total operated patients	200	
Total operated for suppuration	81	40.5
Total with complications of hemo- or hemopneumothorax	82	41.0
Total with suppurative complications of hemo- or hemopneumothorax	53	65.0

REPRESENTATIVE ROENTGENOGRAMS

Figures 1-2 and 3 illustrate hemothorax without suppuration. Hemothorax with suppuration is shown in Figures 4–5 and 6.

FIG. 1-A 1-B 1-C



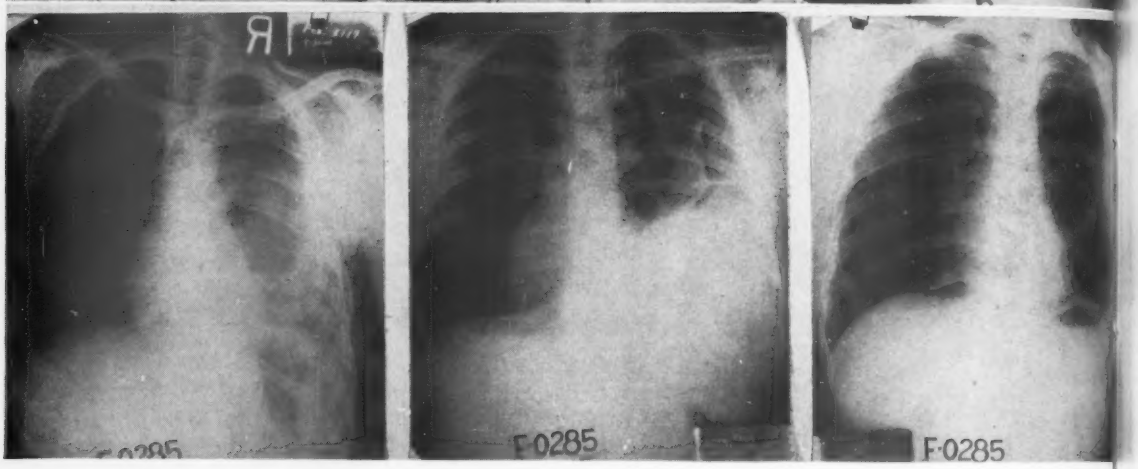
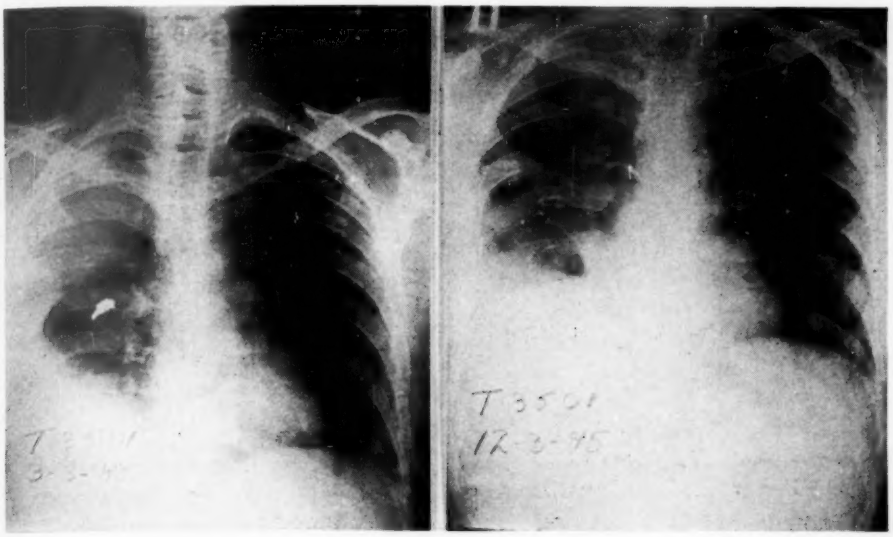


FIG. 2-A 2-B 2-C

FIG. 1.—L-0781: Injured: August 1, 1944. Penetrating wound of right chest.
A.—August 8, 1944. Constrictive pleuritis (clotted massive hemothorax).
B and C.—October 15, 1944. Result 33 days after decortication. Contaminated with *Staphylococcus aureus.*

FIG. 2.—F-0285: Injured: August 23, 1944. Multiple rib fracture with left hemothorax.
A.—August 30, 1944. Left hemothorax.
B.—September 19, 1944. Multiloculation after instillation of air.
C.—September 30, 1944. Result after intensive aspiration, penicillin and thoracic exercise for 10 days.

significant rôle in delaying suppuration. This has flared up when discontinuation of sulfa-drugs and penicillin, clotting or reinfection through fistulae have recreated the essentials for progress. Blanket use of these drugs has been no substitute for sound surgical procedure in this problem. Further subdivision of persistent hemothoraces is based upon characteristics which have seemed to justify some regimentation of treatment.



A B

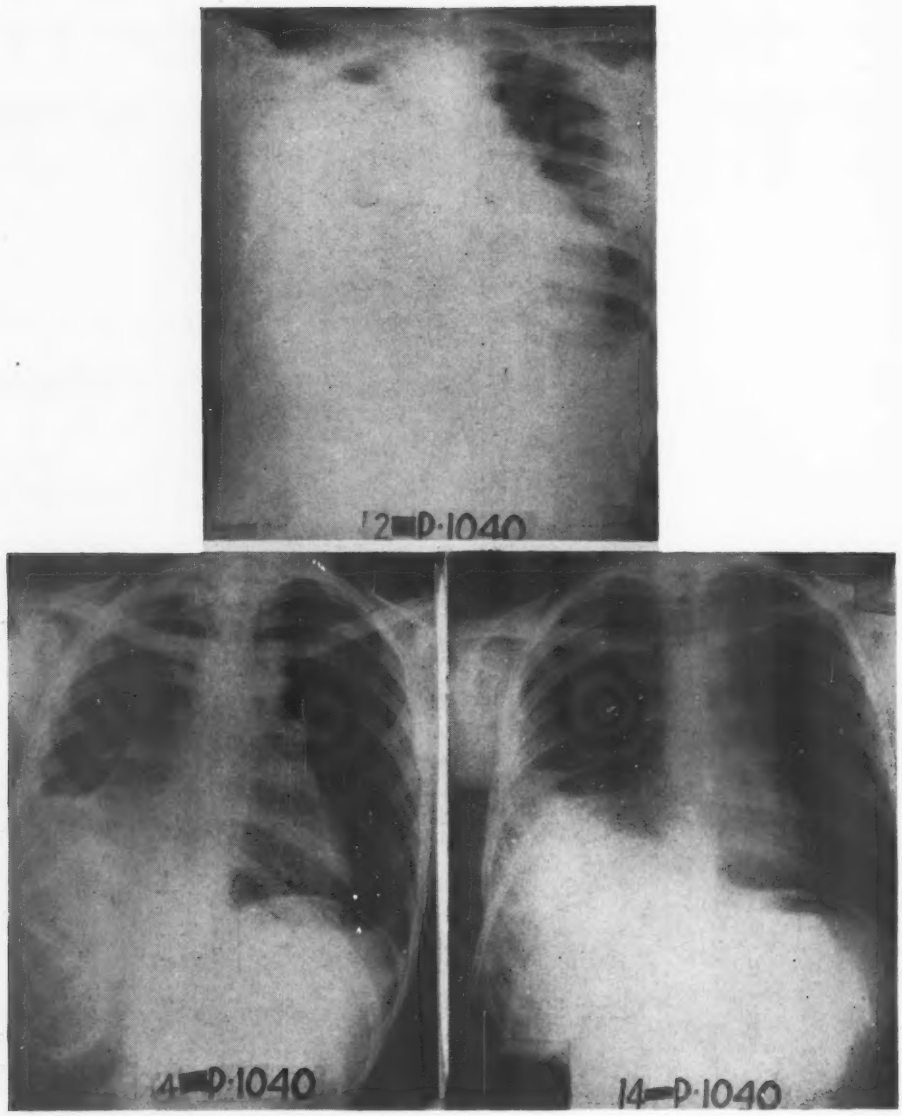
FIG. 3.—T-3501: Injured: February 7, 1945. Penetrating wound right chest. Retained shell fragment right lung.
A.—March 3, 1945. Constrictive pleuritis right.
B.—March 12, 1945. Result seven days after decortication.

(A.) Persistent hemothorax or hemopneumothorax in which organization has not precluded expansion by conservative measures.

(B.) Persistent hemothorax or hemopneumothorax in which organization has precluded expansion by conservative treatment. Invasion by pathogenic organisms has generally proceeded to suppuration unless prevented by early surgical intervention. Multiloculated hemothorax, acute empyema, simple constrictive pleuritis (clotted chest) and suppurative constrictive pleuritis represent various degrees in this process. The distribution is outlined in Table II.

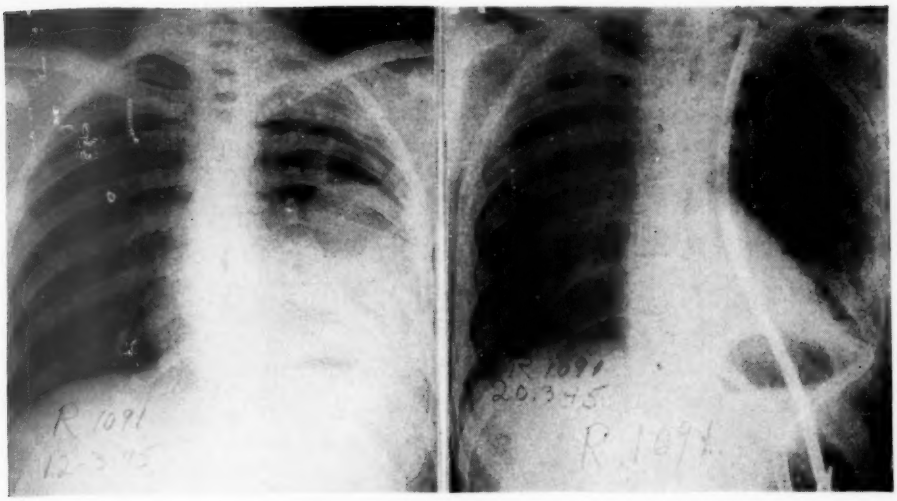
(A.) *Persistent Hemothorax, etc., Amendable to Conservative Treatment.*—With apparent failure of conservative measures in other hospitals, many patients have been referred to the Thoracic Center for operation. Untreated atelectasis and incomplete aspiration have contributed to many of these failures. After careful reëxamination, aspiration drainage of all pleural collections was repeatedly practiced. The air-ways have been cleared by bronchoscopy, cough, postural drainage and other methods. Breathing exercises by the patient have been carefully supervised, rigidly enforced by schedule, and pushed to the

A



B C

FIG. 4.—P-1040: Injured: July 15, 1944. Penetrating wound right chest.
A.—July 26, 1944. Massive empyema, acute. (*Clostridia welchii*).
B.—August 30, 1944. Chronic empyema 30 days after open drainage.
C.—October 30, 1944. Result 25 days after decortication. Tube in small residual basal empyema.

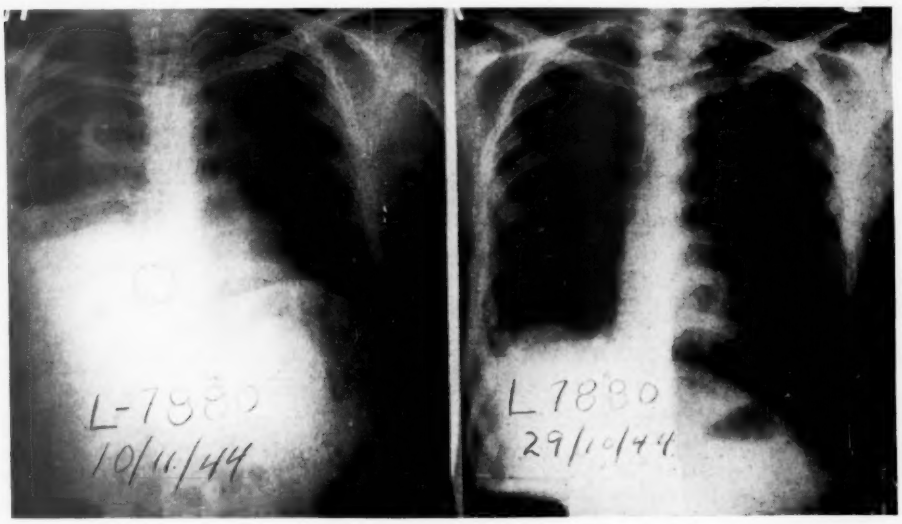


A B

FIG. 5.—R-1091: Injured: February 2, 1944. Sucking wound left chest.

A.—March 12, 1944. Left suppurative constrictive pleuritis. Bronchopleural fistula. (Pyopneumothorax, suppurative hemopneumothorax—*Staph. and Strept.*)

B.—March 20, 1944. Result 24 hours after decortication, segmental resection of left upper lobe and closure of fistulae. Note two tubes for drainage.



A B

FIG. 6.—L-7880: Injured: September 27, 1944. Penetrating wound left chest.

A.—October 11, 1944. Left constrictive pleuritis suppurative. (Pyopneumothorax in clotted hemopneumothorax, *Staph. aureus.*) Subpleural abscess of right lower lobe around retained foreign body (circled).

B.—October 29, 1944. Result 12 days after decortication, resection of abscess area and removal of foreign body from right lower lobe.

limit of tolerance. They have proven to be a valuable adjunct in the therapy and rehabilitation of all chest cases.

The presence of pathogenic organisms did not confuse the issue. The report of positive cultures in 10 per cent of the cases is likely low, due to previous use of penicillin. If pus has not been obtained, surgical intervention, perhaps necessary later, has not been indicated immediately. Aspiration drainage with instillation of 40,000 units of penicillin has been continued with excellent results as long as clinical and roentgenographic improvement were observed. No patient has been considered for operation unless a static or regressive course has been proven after thorough trial (10 to 14 days) on such a regimen. Persistence in the use of these methods has increased the number of patients who, recovering without operation, have returned to duty.

(B.) *Persistent Hemothorax Amenable Only to Surgical Treatment.*—The segregation of these cases has permitted early operation, which has reduced procedural difficulties incident to delay.

Multiloculated Hemopneumothorax.—Not only have few badly-loculated hemopneumothoraces responded to aspiration but many have clotted and suppurated. They represent the earliest stage of simple constrictive pleuritis with which they are grouped. They have been decorticated promptly, at which time ease of operation has been equalled by excellence of results.

Acute Empyema.—The poorly-treated hemothorax has provided a fertile field for the development of acute empyema. The 14 cases of acute empyema which have been admitted to the center comprise 17 per cent of the 82 cases submitted to surgery for complications of hemothorax. All have exhibited certain characteristics. Initial injury had been considered to warrant only simple wound closure in all except four cases. Minimal hemothorax had had uniformly poor aspiration and chemotherapy. Only two had been primarily drained. Five had retained metallic pleural foreign bodies. These conditions had contributed to the onset of empyema of acutely clinical type and of relatively small size. Pus had developed in all cases within 12 to 14 days after injury, and contained the organisms listed. Closed drainage soon after admission was converted in ten days to open-type, with rib resection in ten cases. Initial rib resection and open drainage were used in four cases. All intrapleural foreign bodies were removed at the first operation, regardless of the type of drainage instituted. The local and systemic use of penicillin has not appeared to add much to adequate dependent drainage, and has not been routine. All patients recovered but few were completely healed in less than 60 days after injury.

Early suppuration in extensive hemothoraces has been surgically drained in many hospitals along the line of evacuation. They have reached the Center in good condition for residual care. However, five chronic empyemata required decortication at the Center because of premature, ill-advised or poorly-executed open drainage.

Constrictive Pleuritis (Clotted Chest).—This diagnosis was substantiated by surgery in 29 cases and necessitated 35 per cent of the operations for com-

plications of hemothorax. Bullets (3) and shell fragments (26) had caused sucking wounds in 13 (44 per cent) of them. Only two had been primarily explored and three primarily drained. Metallic foreign bodies were free in the pleural space in two and sealed off in the lung in sixteen. Dyspnea has been the outstanding symptom; signs and roentgenograms have varied. Complete blotting out of the lung, multiple fluid levels, definite demarcation of the clotted area, and retraction to the affected have been typical. The contracted and immobile fused chest has usually not fully developed before 21 days after injury.

All were decorticated in an average of 35 days after trauma. Metallic foreign bodies and large rib fragments were uniformly removed from the lungs and pleural space. Small multiple rib fragments sealed-off in the lung were not disturbed. Two small pieces of metal were recovered by bronchoscopy and cough. Positive cultures were found in eight, or 27 per cent, of the cases. Five of these occurred with retained foreign bodies. All wounds healed by primary union. Twenty-seven patients were well, with closed, healed and non-draining chests after seven days. Two patients developed small collections of pus which cleared with early drainage. All were discharged for major rehabilitation in an average of 44 days after operation unless contraindicated by additional thoracic complaints.

Constrictive Pleuritis (Suppurative).—Suppuration complicated 39 cases of constrictive pleuritis. These represent 48 per cent of the operations for sequelae of hemothorax. These patients have generally been the more seriously injured. Sucking or open wounds caused by larger missiles occurred without exception. Hemopneumothorax rather than hemothorax had resulted in 34 (87 per cent) of the cases. Tension recurred in 11 (31 per cent). Many were multiloculated. Twenty, or 51 per cent, had persistent bronchopleural fistulae through which constant reinfection was probable.

Methods to combat the difficulties have not been uniformly successful. Intermittent aspiration and the flutter-valve have been most ineffective. Only 12 had been primarily explored and 11 drained. Original basal catheters have been too small, poorly placed and removed too early. Foreign bodies had been allowed to remain in eight (20 per cent) pleural spaces. Such bodies in eight (20 per cent) lungs were associated uniformly with bronchopleural fistulae. Abscesses occurred along six of the tracts and around one fragment. Surgery for simple constrictive pleuritis had been delayed in many until frank suppuration had appeared and increased the difficulty of operation.

All these patients were decorticated in an average of 58 days after injury. Preliminary closed drainage of eight cases (20 per cent) with a large tube has controlled excessive sepsis satisfactorily. Decortication has followed in about 14 days. All large metallic and other foreign bodies have been removed from the pleural space and lung. Ten segmental resections were completed for four abscesses and six fistulae. Three superficial small abscesses and 14 fistulae were excised and closed with reconstruction of pleural continuity.

Of 39 cases, 31, or 79 per cent, were completely healed with closed non-draining chests and expanded lungs in seven days. Eight patients (20

TABLE III

CORRELATION OF SIGNIFICANT DATA ON 82 CASES OPERATED UPON FOR COMPLICATION OF HEMOTHORAX OR HEMOPNEUMOTHORAX

		Forward Area					Thoracic Center								
Diagnosis	Case No. & %	Suck. or Open Wd.	Exploratory Thoracotomy	Closed Drain	Retained Foreign Body Pleura	Retained Foreign Body Lung	Closed Drain	Open Drain	Decortication	Fistula and Abscess	Segmental Resection	Days Post-trauma	Wound Infection	Secondary Empyema	Days Postoperative Rehabilitation
Acute empyema	14 17%	9	4	2	5	1	10	14	0	3-F*	0	17	0	0	60 plus
Constrictive pleuritis—simple	29 35%	13 44%	2	3	2	16	0	0	29	0	0	35	0	2 7%	44
Constrictive pleuritis—suppurative	39 48%	39 100%	12	11	8	8	8	0	39	20-F* 51% 5-A† 12%	8	58	2	8 20%	42

*F—Bronchopleural fistula.
† A—Abscesses.

per cent) developed small localized collections of pus which were usually healed 21 days after drainage. Only two wounds failed to heal by primary union. One of these required opening but was successfully reclosed in ten days. Those without other injuries were ready for discharge in an average of 42 days after operation.

Some observations deserve summary:

In 200 consecutive operated admissions, 82 cases (41 per cent) required surgery for some form or complication of hemothorax or hemopneumothorax. Suppuration played the major rôle in 53 (65 per cent) of these. Twenty-nine (35 per cent) remained as simple constrictive pleuritis, although eight were contaminated. Of the 82 only 18 had been explored and 16 drained.

Minimal hemothorax has usually recovered with conservative measures. Early neglect has led to a few localized acute empyemata which have yielded to drainage. Clotting in major hemothoraces has followed failure to completely clear the pleural space. Severe initial injury, retained foreign bodies and bronchopleural fistulae have contributed prominently to late suppuration.

A variety of factors are important in the extensive use of decortication. Gas, oxygen and ether anesthesia with endotracheal technic has proven indispensable. The writers wish to emphasize the invaluable contribution of the anesthetist's comprehensive management of respiration, circulation and allied problems. Without this, the extensive and definitive surgery which has replaced half-measures, stage-operations and long convalescence would never have been possible.

Incision, usually through the 5th, 6th or 7th intercostal space with rib

division at both ends, has insured adequate exposure. After evacuation of the pleural space, the limits at which the membrane is reflected from lung to the chest wall have been defined. To avoid laceration, the lung has been progressively mobilized toward the mediastinum as the rib-spreader is gradually opened widely. Removal of the tough constricting membrane from the entire lung, most of the chest wall and diaphragm has been a tedious procedure, frequently consuming four hours. Delay has invited infection and both have increased the difficulty of removal. The observation that mobilization of the entire lung has allowed it to expand more rapidly and normally has been substantiated by postoperative roentgenograms, and results. Such mobilization, regardless of extent of pleuritis, is now routine and deemed of vital importance in the speed and completeness of recovery which these patients have had. At least two multiple-holed catheter drains have been inserted routinely apart from the incision and have been sutured in place intrapleurally. One ascending anteriorly to the apex has insured evacuation of air without trapping around the upper lobe which, with rare exception, has expanded well. Another in a horizontal position in the upper limits of the costophrenic sinus has prevented early dependent accumulation of fluid. A third, suitably placed, has drained the gutter or site of marked suppuration or lung resection when necessary. After the instillation of penicillin (100,000 units in 15 cc. of saline) particularly around suppurating and resected areas, the chest has been carefully closed in layers. Divided rib ends and the ribs adjacent to the incision have been closely approximated by wire through drill holes. This, with anatomic repair of all soft tissue has given excellent wounds. After application of dressings, but just before removal from the table, suction of the catheters and bronchoscopy have permitted immediate lung expansion and practically eradicated tension pneumothorax and atelectasis.

Decortication has been carried out as soon as the diagnosis and a static or regressive state have been proven. The extensive empyemata which have occurred as the result of infection of previously persistent and clotted hemothoraces have always been chronic at inception. Simple drainage has been used in them only as a preliminary measure to improve poor clinical condition. Decortication has offered the only possibility of cure without protracted convalescence and multiple operations.

Several factors have favored the success of this procedure.

Meticulous attention to surgical technic with adequate exposure, visual dissection, gentleness with all tissues and thorough hemostasis have warranted the time spent. Fine interrupted cotton suture material has been used exclusively, without the appearance of any objection.

Decortication has been supplemented by any other procedure considered necessary to maximally approximate normal thoracic relations. Foreign body removal, closure of fistulae, resection of lung, repair of hernia, obliteration of dead space and reëstablishment of pleural continuity have been uniform practices. Small superficial abscesses and fistulae have been excised and sutured

without parenchymal drainage. Large ones have been segmentally resected and closed with additional pleural drainage at the site.

Maximum preservation and reconstitution of the chest wall by intercostal incision and subsequent wiring through drill holes have preserved maximal functional apparatus and unity action of the wall in these frequently "shot-up" chests. Troublesome pericostal sutures have been avoided. These have perhaps enhanced the benefits of thoracic exercise which can and should be instituted postoperatively within 24 hours.

The ability to obtain and maintain prompt expansion of the lung, obliterate the pleural space and prevent accumulation of blood or other culture media have contributed most to the success of this procedure. Operation has not been considered complete until this could be done and all defects leading to the original condition corrected. In maintaining such conditions, multiple closed catheter drains have worked quite satisfactorily, and high negative pressure from suction pumps has not seemed necessary. They have been retained until clearing of the chest has signified obliteration of the pleural space from expansion. This has usually taken four to five days, during which time gentle irrigation with penicillin (250 units per cc.) has maintained patency of the tube. On few occasions they have been left in place as drains of small collections and gradually withdrawn with tract irrigation. Intrathoracic penicillin has inhibited infection in the ever-present minimal fluid which collects in spite of drainage. Intramuscularly (120,000 units daily for five days), it has protected the wound until body forces can take over complete control.

Results have been considered good enough to warrant further trial of these procedures. Empyemata amenable to classical drainage methods have been in the minority in this Center. The ability to obtain a closed nonsuppurating pleural space in less than 14 days in 80 per cent of patients operated upon for suppurative constrictive pleuritis has influenced the writers to use decortication increasingly. The recurrence of empyema in 20 per cent of them has not been considered a valid objection, since they have been small and have responded well to prompt drainage, with a marked reduction in the duration and severity of illness. No chest wall phlegmons nor other feared sequelae have arisen. These results have seemed to further justify the prompt use of decortication immediately after clotting to avoid the risk of suppuration. By some this has been called radical surgery. Yet in this series, 75 decortications, many in the face of severe infection, have carried no mortality, and the number continues to grow in this as well as all other Thoracic Centers. Although the closed chest may be a boon to medical personnel, it has been little short of a blessing to patients and most gratefully received by them. Neither early neglect of conservative measures nor retreat before the misnomer, "radical surgery," should deny promise of cure to any patient. One can look forward to less decortication and better results from more preventive surgery at the forward stations rather than by adoption of less satisfactory measures in the Centers.

(TO BE CONTINUED)

WAR EXPERIENCES WITH THE NONSUTURE TECHNIC OF ANASTOMOSIS IN PRIMARY ARTERIAL INJURIES

CHARLES F. STEWART, M.D.
NEW YORK, N. Y.

THE PRESENT COMMUNICATION is concerned with the problem of restoring blood flow through arteries damaged by missiles. Seven cases are reported here in which a nonsuture technic was attempted. The casualties were treated in an American Evacuation Hospital in the recent European War.

As is usually the case in war-time, the desire to restore the functional continuity of arteries became to us a problem of pressing and intriguing interest. We were fortunate in having the timely advances of Blakemore, Lord and Stefko[1] as the basis for our attempts. The devices with which surgeons have tried to repair arteries have been many in the past, and it is said that every sort of tubular structure from goose quills to chicken bones has been used. During World War I Tuffier[2, 3] had some success with a silver plated tube coated with paraffin. Makins[4] reported some good results with this method, and one specifically through which the distal pulsations were maintained for as long as ten days. The Carrel vein graft technic[1, 4, 5] was sometimes satisfactory in the last war, but was technically difficult, time-consuming, and very subject to thrombus formation. Direct arterial suture,[5, 6, 7] as stated by Leriche and Werquin,[8] is generally impossible in war wounds. It is tedious and difficult. Ragged tears and loss of substance may make even the apposition of the arterial ends impossible. Local thrombosis frequently follows the repair.[27] Besides these initial factors, suture is dangerous in a war wound which is left open, as hemorrhage is apt to occur. Infection is still too often present, and, finally, there may be little or no support of the vessel by healthy adjacent tissues. Mitchiner[9] stresses the complications developing late in patients after arteriorraphy in World War I; frequently these men developed aneurysm at the site of suture. Yet when a primary artery is simply ligated, and its continuity is not restored, the extremity may be lost due to ischemia, or there may be functional limitations evident later.[28, 30, 31]

In reviews of the subject in 1939 and 1940, Maurer,[10] and Mitchiner,[9] respectively, gave rather unhappy pictures of what could be expected in vascular surgery in battle casualties. Only under the most perfect conditions could they give any hope of preserving the function of an artery by direct suture. Yet these conditions seldom obtain in warfare, and even then may be followed by late complications. In the early part of American participation in this war, we were impressed by the unprecedented loss of limb due to ischemic gangrene. In the Tunisian campaign, 100 per cent of our cases requiring ligation of the popliteal artery came to amputation. These observations were confirmed by others,[11, 27] and attributed to the increased explosive effect of modern missiles. It became more important than ever to find a method to save these limbs. It had to be a method which would restore arterial blood

flow, which would rarely cause thrombosis, and one that would be relatively free of the reported late complications. The nonsuture method advocated by Blakemore, and associates,[1, 11, 12, 13, 14] seemed to fulfill the prerequisites.

Blakemore and Lord[1, 12] at first sought a tubular structure to act as a prosthesis, and chose a Vitallium tube which could be inserted into the divided ends of the artery. This was done experimentally both with the ends of the artery sutured in continuity (Fig. 1 A), and with them distracted and ligated over the ends of the unlined tube (Fig. 1 B). The results of this method were

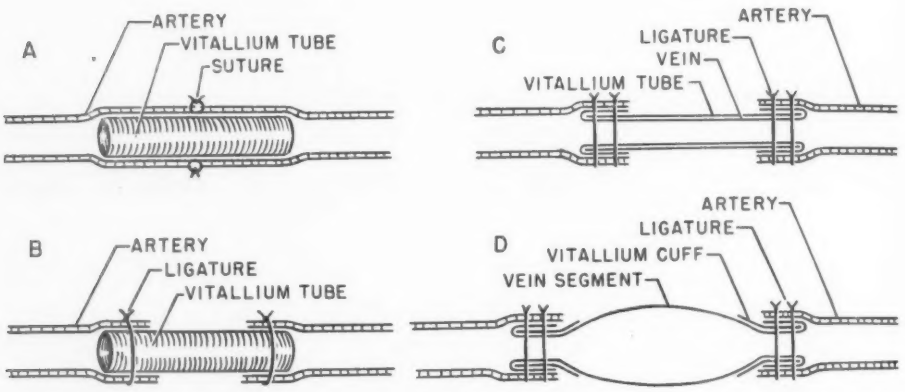


FIG. 1.—(A) Experimental: artery sutured in continuity over an unlined Vitallium tube. (B) Experimental: artery ligated over an unlined Vitallium tube with arterial ends separated. (C) Clinical: vein-lined Vitallium tube ligated in place to bridge arterial defect. (D) Clinical: vein segment reflected over Vitallium cuffs shown connecting arterial ends.

unfavorable in that only one in nine, and one out of six, respectively, were successful. Another method tried—without the use of anticoagulants—was that of reflecting the ends of the artery over metal cuffs and uniting them with a vein graft. Little success came of this plan either. The final development was the use of a Vitallium tube lined with a vein segment which overlapped the ends of the tube; this graft could be inserted into the artery with intima of vein in contact with intima of artery (Fig. 1 C). The prosthesis was held in place by two ligatures at each end. A modification of this, to bridge longer arterial defects, was the two-tube method (Fig. 1 D). In this, the vein was similarly applied, but using only a cuff of metal at either end with the interposed segment of vein not encased in metal. Both of the latter methods were highly successful experimentally, and were later applied to civilian vascular injuries, aneurysms, and other conditions, with excellent results.

We attempted the nonsuture technic in seven cases. The average time in getting these patients from the battlefield to the operating room was 12 hours and 50 minutes; the earliest one was three hours and 40 minutes. More forward installations, the Field Hospitals, devoted their time almost exclusively to critically wounded patients: Those with abdominal, chest and head wounds.

Entry to our hospital was frequently only a few hours after injury, but two factors delayed operation—the sometimes prolonged treatment of shock, and the precedence given to patients more desperately wounded. Usually the time required to get the patient ready for operation after admission was equivalent to that taken in his transportation to the hospital. Recognition of vascular injuries in war casualties was often difficult. Many times men with extremity injuries who were in shock would have very cold, pulseless limbs, all or several of which would return to normal color, temperature and function with the adequate treatment of shock. Often the presence of a vascular injury could only be suspected after shock treatment when the extremity with vascular damage failed to return to normal. Associated severe injuries usually made the treatment of shock unduly prolonged. As some authors had predicted, the war injuries were often extensive, leaving scant muscular support for an arterial anastomosis. All of the wounds were perforce left entirely open. Not even the vascular sheath was closed. Frequently, some degree of infection developed after operation, endangering the anastomosis. Collateral vessels were often severely traumatized. Major A. F. McBride observed that collateral blood supply seemed better in cases in which one or several of the large peripheral nerves was not functioning. Makins,[4] in contrast, states that associated nerve injuries favor the development of gangrene in a limb suffering an arterial injury. Some of us, in accord with McBride's opinion, were led routinely to inject the nerves in the affected extremity with novocaine. Sometimes, even where a lumbar sympathetic ganglion block had been done first, the peripheral nerve block seemed to improve the circulation of the limb. Fractures of the long bones were frequently associated with the vascular injuries and made anastomosis somewhat more hazardous, particularly in the femur where application of a hip spica was apt to put a strain on the prosthesis. Occasionally the graft lay directly on a fracture site.

On admission to the hospital, all of the seriously injured patients were treated in the shock ward. They had had first-aid treatment before entry. Broken extremities had been immobilized, usually in a Thomas splint. Sulfanilamide powder had been put in the wounds. Some of the vascular patients had pressure bandages on their wounds, others had tourniquets. Many of the patients with whom we are concerned were in severe shock. These were treated with plasma until blood was available; plasma alone was not enough.[17] Massive blood transfusions were given. When an extremity failed to give an appearance of viability after intensive supportive therapy, it was suspected that there was vascular damage to the primary artery and perhaps to collaterals. In such cases, when the primary vessel was found at operation to have been severed or thrombosed, the main collateral vessels were inspected, where possible. If they had been injured, a prosthesis was used. In some instances where it was feared that exposure of the collateral would disturb functional capacity, the decision to use or not to use a prosthesis was dictated by the clinical condition of the extremity. It must be stressed here that when collateral supply as well as the primary artery is damaged, every effort should

be made to reëstablish functional continuity of the vessel. Ideally, an anastomosis should be done in all cases, as a limb supported only by its collateral is so frequently subject to easy fatigue, intermittent claudication, and is generally less competent than the normal one.[28, 30, 31] In our early war experience[11] we were surprised at the failure to survive of many limbs in which the prognosis was thought good. It was some time after that that we acquired the metal tubes essential to the nonsuture technic. Hence, many cases went through our hands before we accumulated the experience and the material with which to try this procedure.

CASE REPORTS

Case 1.—An American soldier with two gunshot wounds, one in the abdomen and one in the left thigh. Wounded at 10:00 A. M. November 13, 1944, at Montidaly, France. On admission to our hospital, a tag of omentum was seen protruding from an abdominal wound. Both lower extremities were so cold that it was impossible to note any difference in temperature between them. A vascular injury was not seriously considered. There was no evidence of a fracture of the left femur. B.P. 90/65; P. 100.

Operation.—Major William H. Cassebaum: 4:30 P. M. November 13, 1944.

Pathology: (1) A penetrating wound of the left buttock entering the pelvis, with lacerations of the lateral wall and apex of the bladder intraperitoneally. The tract made its exit suprapubically without injury to any other abdominal viscus. There was a severe compound comminuted fracture of the left superior pubic ramus. (2) A perforating wound of the left thigh with contusion and thrombosis of the superficial femoral artery about 12 cm. below the inguinal ligament. The missile had entered posteriorly and came out anteriorly in the upper third of the thigh.

Procedure: (1) Exploratory celiotomy through a left paramedian incision, with findings as described. Closure of the two perforations of the bladder followed by cystostomy with a catheter. The left first and second lumbar sympathetic ganglia were excised. Débridement of the fractured pubic ramus was carried out. The abdominal incision was closed in two layers. (2) Débridement of wounds of the left thigh. The femoral artery was then isolated: the thrombus and clot were removed through a longitudinal incision in the artery. Damage to the intima was seen but the artery wall was sutured. When control from above was released, a little blood leaked from the arterial suture line, and in a short while the artery seemed thrombosed again. Hence, the thrombosed section was resected, together with a section of the femoral vein. An anastomosis, using the vein segment and Vitallium tube, was attempted. The lower end of the prosthesis, however, pulled out of the artery while the upper end was being inserted. As the patient's pulse was 160 at that time, it was considered unwise to persist. Both ends of the artery were ligated. The distal arterial end bled slightly before ligation. Operating time three and one-half hours. From admission to completion of operation, the patient had received 2,500 cc. of whole blood.

Course.—November 17, 1944: Considerable pain in the affected leg for past two days. The foot was obviously dead, the calf tender and tense. Sensation to pinprick was noted as dullness to within three inches of the ankle. There was no sensation in the foot. "We have not been able to restore his blood volume for fear of damaging his liver or increasing the existing jaundice, which must certainly be due to transfusions."*

* We had many reactions—jaundice, pyrexia and hemolysis—resulting from massive blood transfusions. Most of these were in Group A recipients and seemed to occur after more than 1,500 cc. of pooled plasma or Group O blood. Type specific transfusions (*i.e.*, A donor to A recipient) completely eliminated this reaction. I hope Captain George H. Parks will report further on this subject).

Second Operation.—6:00 A. M., November 17, 1944.—Guillotine amputation of the left leg below the knee. The skin and gastrocnemius muscle bled moderately; and the latter muscle was of good color. The other muscles of the lower leg were grayish-purple and did not bleed. The anterior tibial muscles were "almost white."

Case 2.—An American soldier suffering from a shell fragment wound of the left leg received at 3:00 P. M. November 13, 1944, at Leintry, France. Examination on admission revealed a patient in profound shock. B.P. 85/35; P. 120. There was a perforating wound of the right leg with entry on the medial side of the knee at the patella, with the wound of exit about four inches above the knee cap on the lateral aspect of the thigh. Only slight movement of the toes and foot was noted. A dorsalis pedis pulse was said to be perceptible on admission (this was questioned). Roentgenograms revealed a fracture of the medial condyle of the femur extending into the joint. Patient's condition was good at 10:00 P. M. 1,200 cc. of blood and 750 cc. of plasma were given preoperatively.

Operation.—Major Andrew F. McBride, 4:00 A. M. November 14, 1944.

Pathology.—Severe shell fragment wound of the right lower thigh; traumatic arthrotomy of the right knee joint, with a complete compound comminuted fracture of the medial condyle of the femur. Severance of the tibial and peroneal divisions of the sciatic nerve. Division of the popliteal artery and vein. Absent distal pulsations; the popliteal pulse was absent with the patient under anesthesia. The affected foot was cooler than the well foot and insensible to stimuli.

Procedure.—A sciatic nerve block was done first. Exploration of the popliteal space was performed through a midline incision with a tourniquet fastened on the upper thigh. The vessels and nerves were exposed and found divided at a level believed to be between the superior and inferior geniculates. The popliteal artery was damaged from 0.5 cm. to 1.0 cm. beyond each divided end, and the ends were filled with thrombus. Two attempts were made to interpose a venous transplant with two metal cuffs. The great saphenous vein was used. The lower end of the transplant was hitched up first, and with release of the tourniquet there was a steady drip of blood from the distal artery through the vein segment. The prosthesis, however, came out when connected to the proximal end of the artery. A second attempt at union was successful at both ends, but after ten minutes the arterial pulse forced the transplant from the artery. The artery was then ligated. Nothing was done to the knee joint at this time. Plaster encasement applied. A sympathectomy was not done in view of the nerve section. 1,000 cc. of blood was given during operation. The operating time was three hours and ten minutes.

Course.—The leg became progressively more necrotic and an amputation through the lower third of the right thigh was done 46 hours after the first operation.

Case 3.—A German prisoner with a gunshot wound perforating the left thigh and penetrating the right thigh. Wounded at 8:00 A. M. February 1, 1945, near Colmar, France.

Examination of the patient revealed a 1 x 1 cm. wound on the posterolateral aspect of the left thigh at the junction of the middle and lower thirds. There was a 20 x 10 cm. wound of the anteremedial surface of this thigh. An obviously severely fractured femur complicated the situation. The sensibility to pain and touch were diminished in the affected foot. This foot was cold, pale and slightly cyanotic, with no pulse palpable. Circulation was described as "almost *nil*," yet the foot was not dead. There was an 8 x 3 cm. wound of the right thigh.

Operation.—Captain Charles F. Stewart, 2:00 A. M. February 2, 1945.

Pathology.—There was wide destruction of the vastus medialis muscle and less marked damage to the biceps femoris and adductor magnus. A complete compound comminuted fracture of the femur was associated with this perforating wound. The superficial femoral artery had been divided about 5 cm. above adductor hiatus. Division of the femoral nerve was noted.

Procedure.—Débridement of the skin, fascia, muscles and bone. Part of the femoral

vein was resected. An anastomosis of the severed femoral artery was accomplished with Vitallium cuffs, using a segment of the femoral vein. (At first a segment of the saphenous vein was tried but was found to be too small in caliber.) A good stream of blood came through the free distal end of the vein segment with the proximal end fixed in place. Anastomosis was difficult because the cuffs slipped out of the artery both before and after they were ligated. Finally, the anastomosis was satisfactorily accomplished with a cuff 4 mm. in diameter above and one 3 mm. in diameter below. There was a palpable pulsation of the artery below the anastomosis. The completed bridge lay immediately against the fracture of the femur. The sciatic nerve was blocked under direct vision in the posterior wound. Five Gm. of sulfanilamide were placed in the wounds, which were left entirely open. The foot was warmer after operation; the calf muscles, however, were slightly firm. After the necessary manipulation of putting on a hip spica, the foot again became pale and cold. Operating time five hours.

Course.—February 2, 1945, 7:00 P. M. The left foot was warm but not as warm as the right. No feeling in the foot (nerve division and block) nor ability to move it. Temperature 102.4° F. at 4:00 P. M.

February 8, 1945: Fever, up to 101.2° F. The left foot was warm but considerably mottled and slightly bluish. No pulse palpable.

February 10, 1945: Foot warm. No pulse palpable. Could move toes moderately well. Patient evacuated to the rear February 12, 1945. Condition unchanged.

Final note: (by letter from the General Hospital to which the patient had been evacuated.) "The patient was received on February 12, 1945, in fairly good condition. The day following admission he had a small pulmonary embolus, with classical chest pain and hemoptysis. The left leg was of good color and remained so; no edema. Due to the embolus, no studies (arteriograms) were made, as you suggested. His condition was improving, but he suddenly had a large pulmonary embolus on February 26, 1945, and expired. Autopsy showed thrombosis of the left femoral artery; however, it must have remained patent for some time until collateral circulation was established because of good color and warmth of the extremity. The source of the pulmonary emboli was the left internal iliac vein. The patient's condition was never good enough to warrant examination of the wounds (hip spica) or any type of surgery."

Case 4.—An American soldier wounded at 11:00 A. M. February 5, 1945, by a shell fragment perforating the upper third of the left thigh.

On examination, the patient was found to have a 4 x 4 cm. wound on the anterior aspect of the thigh below the inguinal ligament, lateral to the femoral canal. The laceration was surrounded by a zone of swelling. The left leg and foot were quite cool, and the muscles of the thigh and leg were firm. No pulse could be felt in the foot. There was no evidence of fracture or of nerve injury. 500 cc. of plasma and 500 cc. of whole blood were given preoperatively.

Operation.—Major William H. Cassebaum. 6:00 A. M. February 6, 1945.

Pathology.—There was a thrombus in the femoral, the profunda femoral and the lateral femoral circumflex arteries. In the anterior wall of the femoral artery there was a slit a few millimeters long. The walls of the involved vessels were severely contused with resulting subadventitial hemorrhage. The wounds were very dirty.

Procedure.—The wound over the femoral artery was extended upward. A plasma tubing clamp was placed on the femoral artery proximal to the injured portion. The small slit in the femoral artery was enlarged and the thrombus and clot was removed, by milking it out from below. Some bleeding from below then became apparent, and the blood flow was controlled from below. A portion of the femoral vein was excised, reversed and transplanted into the artery after having been passed through two Vitallium tubes each about one inch long. After joining the anastomosis, no pulsation of artery distally became apparent. The wound was débrided. Little or no bleeding was encountered in the sartorius or quadriceps femoris muscle. Woolen material (clothing fragments) was removed from the wound. A considerable amount of venous bleeding was noted. After

operation the leg still appeared cold and dead. Gas gangrene was feared because of destruction to collaterals and the extensive contamination of the wound.

During operation the patient received 1,000 cc. of 5 per cent glucose in saline, and 1,500 cc. of whole blood.

Course.—February 7, 1945. 7:00 A. M. Thigh swollen and gas present.

Second Operation.—February 7, 1945. 8:45 A. M. High thigh amputation of the left lower extremity. Clot occupied the vein graft, though when this was later removed the system was patent to water from a 30-cc. syringe under pressure of the weight of the plunger.

Case 5.—An American lieutenant with a severe gunshot wound of the right thigh received at 7:30 A. M. April 8, 1945. Admitted at 5:20 P. M.

Examination.—B.P. 125/80; P. 88. The patient had a large hematoma of the right thigh with an hemarthrosis of the right knee. General condition very good. The leg was in a Thomas splint. Motion of the toes was good; posterior tibial pulse feebly palpable. 1,000 cc. of 5 per cent glucose in saline and 500 cc. of blood were given the patient prior to operation.

Operation.—Captain George Crawford. 3:30 A. M. April 9, 1945.

Pathology.—A compound comminuted fracture of the right femur with laceration of the upper third of the popliteal artery. Good pulsations of the dorsalis pedis and posterior tibial arteries were noted in the operating room, but these disappeared just before the patient was anesthetized.

Procedure.—The wound on the laterosuperior aspect of the knee was opened and large blood clots were evacuated. The surrounding muscle was infiltrated with clotted blood. In its superior portion the knee joint had been pierced. Irrigation of the knee joint with saline was followed by the instillation of 10,000 U. of penicillin and closure of the capsule. On evacuation of blood clot from the thigh wound profuse hemorrhage was encountered; hence, the popliteal artery and vein were exposed. An incomplete tear was found in the upper third of the popliteal artery. The tear measured 2 cm. in length and encompassed two-thirds of the circumference of the vessel. A section of the popliteal vein was taken, threaded through a cannula which was placed in the torn popliteal artery. Upon release of the tourniquet, and after dissecting the adventitia off the superior end of the artery, a pulsation was felt in the distal segment. Sulfanilamide powder was dusted into the wound. A Tobruk splint was used. A right paravertebral sympathetic block was done with 2 per cent novocaine. The foot was warm and of good color after the operation.

Course.—April 10, 1945: Foot warm and of good color but no palpable pulse.

April 11, 1945: Pentothal anesthesia; wound inspected. The popliteal artery was palpated. A definite pulsation was palpable below the anastomosis. Tobruk splint replaced by a plaster hip spica.

April 14, 1945: Good dorsalis pedis pulse palpable.

Case 6.—An American soldier suffering from a penetrating shell fragment wound of the right arm received at noon on April 25, 1945. He was admitted to this hospital at 6:45 P. M. On examination, a penetrating wound of the lower third of the lateral side of the right arm was seen; in the anterior axillary fold the skin had been torn slightly and the foreign body lay in the right pectoral muscles. No pulse was palpable in the right wrist and there was paralysis of the three major nerves. B.P. 120/60; P. 120. The forearm and hand were pale but not cold. The fingers were flexed and stiff. Some capillary circulation was thought to be demonstrable.

Operation.—Captain Edmund R. Taylor and Captain Charles F. Stewart. 10:20 P. M. April 25, 1945. B.P. 116/82; P. 138.

Pathology.—Wound as described, with severe damage to the triceps muscle. A compound comminuted fracture of the midthird of the humerus was revealed. The brachial artery was completely severed just below the origin of the profunda brachial artery. A profuse blood flow came from the distal end of the artery. In addition, the brachial vein

was lacerated. The radial nerve had been completely divided and its ends were frayed for 6 cm. on each side. The median nerve was 30 to 50 per cent divided. Although the ulnar nerve was not functioning, it was thought to be anatomically intact. The profunda brachial artery was divided at the site of the fracture.

Procedure.—Débridement of the wound tract and curettage of the fracture ends. An anastomosis was carried out using a segment of the brachial vein and two Vitallium cuffs. After several attempts to insert a 3-mm. cuff at each end, a 2-mm. cuff had to be used at the lower end. No pulsation in the distal segment could be palpated at the termination of the procedure. All nerves in the wound were injected with 2 per cent novocaine; these were the radial, the musculocutaneous, the median and the medial antibrachial cutaneous nerves. The radial nerve ends were each transfixed, though separated, with a fine wire suture. A shoulder spica was applied. During operation the patient received 1,500 cc. of blood.

Course.—5:45 A. M. April 26, 1945: Cervical sympathetic block, right, with 5 cc. of 2 per cent novocaine. Heparin therapy was started by continuous intravenous drip—the patient receiving 20 cc. of heparin solution in 2,000 cc. of diluent in 24 hours.

10:40 A. M. April 27, 1945: Cervical sympathetic block. Fingers less stiff and cold. In sitting position, the hand veins distended and the color of the hands became pinker. The forearm was warmer and less tense.

6:00 P. M. April 28, 1945: Cervical sympathetic block with 20 cc. of 1 per cent novocaine. Resulting Horner's syndrome. Right hand was mottled and cold. The fingertips were quite blue.

April 29, 1945: Cervical sympathetic block. No change in hand.

April 30, 1945: Hand definitely gangrenous with a line of demarcation at the wrist.

Because of the tactical situation, the patient was evacuated to a General Hospital without his hand being amputated, though it was inevitable.

Case 7.—An American soldier with a gunshot wound of the left thigh incurred at 9:20 A. M. June 18, 1945, at Augsburg, Germany, when the patient was accidentally shot by another soldier. On examination, there was a perforating wound of the lower third of the left thigh. No pulse was felt in the foot, but the foot was warm. Motion of the foot was normal.

Operation.—Major Edgar L. Frazell. 1:00 A. M. June 19, 1945.

Pathology.—There had been considerable bleeding into the muscle planes. The superficial femoral artery, about 1.5 cm. proximal to the superior internal geniculate artery, was 50 per cent divided. The proximal and distal lumina were filled with soft blood clot. Both ends bled on removal of the clot.

Procedure.—The artery was approached from the posteromedial aspect, following the tract of the missile. A plastic tube without a vein-lining was used to bridge the defect, as much of the lateral wall was missing. The prosthesis was sutured (ligated) into place, and the lacerated vessel wall was partially approximated. There was a questionable dorsalis pedis pulse after the completion of the operation. Heparin was started: 30 cc. in 1,000 cc. of saline was given in the first 24 hrs. The sciatic nerve was blocked with novocaine.

Course.—Ten hours postoperatively: The left foot was warm and capable of motion. The posterior tibial pulse was definitely palpable. Blood coagulation time 60 minutes plus.

One week postoperatively: The left foot was warm, viable, and the pulses were easily palpable in the foot. Mild wound infection. Secondary closure of the wound was accomplished on the 14th day. Three weeks postoperatively, with wounds healed, palpable pulses and functioning toes, the patient was evacuated to the rear.

General Discussion.—Seven cases of arterial injury with attempted nonsuture anastomosis have been presented. These are representative vascular injuries, demonstrating division of the artery in three cases, thrombosis in two,

and lateral laceration in two. The limbs of three of these patients survived. Two of the satisfactory results were obtained with vein-lined tubes (Cases 3 and 5), while the third was accomplished with an unlined tube of plastic material (Case 7).[29] Of the failures, the limb in one patient (Case 4) was probably not viable at the time of operation. Two other patients had their arteries ligated after failure of efforts to insert the prosthesis. The remaining case was treated with a prosthesis which was certainly too small.

Three successes in seven attempts makes a survival rate of 43 per cent in this group. All seven cases had severe vascular injuries. It is impossible to state which of these limbs might have survived with ligation alone. All three of the satisfactory cases might have retained a viable extremity without restoration of continuity of the vessel. In Case 6, the loss of limb with ligation alone could have been predicted. Because of the inability to predict survival of limb in all cases of interruption of flow in primary artery injuries, it is safer to insert a prosthesis where possible. Comparison of statistics in so small a series is futile, but for general interest the results of our major vascular surgery in the first half of 1945 may be included. (Dr. Andrew F. McBride will publish later a more complete analysis of all of our vascular cases.) Excluding injuries to any except major arteries, and five of the cases described, our records in 1945 show these results:

Artery Ligated	No. of Cases	No. Amputated	% of Limb Survival
Common femoral	1	1	0
Superficial femoral	14	6	57
Popliteal	8	8	0
Axillary	2	1	50
Brachial	8	1	88

In 1944, the leg survived in only 25 per cent of 16 cases of ligation of the superficial femoral artery, and the limbs in 25 per cent of 12 ligated popliteal arteries survived.

Breaking our seven cases down into location and result, we have:

Artery Involved	No. of Cases	No. Amputated	% of Limb Survival
Common femoral	1	1	0
Superficial femoral	3	1	67
Popliteal	2	1	50
Brachial	1	1	0

When the prosthesis cases are included with the general data for the half-year period, the results are:

Artery Involved	No. of Cases	No. Amputated	% of Limb Survival
Common femoral	2	2	0
Superficial femoral	16	6	63
Popliteal	9	8	11
Axillary	2	1	50
Brachial	9	2	78

Cases 1 and 2 resulted in amputation. Neither of these cases had a prosthesis inserted, merely attempted. Since they were done in 1944, they are not

included in the last table. Inclusion of the prosthesis cases in the statistics for 1945 raises the survival of limbs in superficial femoral artery cases from 57 to 63 per cent, and in the popliteal group from 0 to 11 per cent. Brachial artery statistics fall from 88 to 78 per cent, with the failure of one prosthesis case.

Our difficulties with the nonsuture vein graft technic become apparent from a study of the cases presented. A working knowledge of the method from previous experience or experimental work would have been of great help to us. The crucial and most difficult step in the procedure is the actual insertion of the prosthesis into the artery. Failure in Cases 1 and 2 was due to this factor. It is believed that failure in Case 6 was due to the use of too small a prosthesis. Blakemore[26] recommends the following technic for inserting the prosthesis: (1) Mosquito clamps are attached to the artery end at three or four points. The bite of the clamp includes all layers of the arterial wall for a distance of 1 to 2 mm. Care must be exercised not to tear the thickened, contracted arterial wall. (2) Assistants hold the mosquito clamps, slightly everting the edges of the artery. (3) The operator holds the bare rim of the vein-covered metal cuff in a hemostat. While the loose end is held taut to thin-out the vein, the operator pushes the prosthesis into the end of the artery. Doctor Blakemore recommends that steady constant pressure for a minute or more be exerted while inserting the cuff. This exertion is necessary to overcome the spasm of the arterial wall. Blakemore and Lord have observed a sudden release of spasm during this maneuver, allowing the cuff to slip into the artery. It can be compared to overcoming spasm by steady traction in reducing a dislocated shoulder.[26] In some of our cases, seen long after injury, the arterial spasm seemed almost irreversible. Use of too small a prosthesis, or tearing of the artery wall was apt to result in such cases. To overcome the strong spasm of an artery, dilatation with a small speculum might be of value. Such a speculum should be inserted only 2 to 3 mm. lest the intima be damaged beyond the distance of contact with the prosthesis. The speculum should be used as a very gradual dilator, and should be removed before attempting to insert the prosthesis. Certainly, in the light of present knowledge, preoperative nerve blocks and periarterial stripping[6, 8, 10] should be used in an attempt to dilate the affected artery.

Anastomosis by the described technic requires the lumen of the artery to be impinged upon, or narrowed by, three foreign layers of material. These are the Vitallium tube and two layers of the vein graft. When the vein segment is too large in circumference for the caliber of the cuffs, there will be a certain amount of pouting of the vein wall into the lumen of the prosthesis. This may be enough to be obstructing. To remedy this fault, a vein segment of the appropriate caliber must be used. It should be pulled taut in all axes. A piece of vein that is too small in caliber is equally unsatisfactory. In Case 3 a segment of saphenous vein was prepared for a superficial femoral anastomosis. When taken, this segment was in spasm, and could not be dilated or relaxed enough to provide an adequate lumen. A femoral vein graft was finally used. The required length of any vein transplant is surprisingly great. Doctor Blake-

more[26] has arrived at this method of estimating the length of the vein segment needed: (1) The severed arterial ends are grasped with clamps, as described above, and drawn together with "physiologic" tension (*i.e.*, the degree of tension which would seem compatible with the normal elasticity of the vessel). (2) The resulting gap between the ends of the artery is then measured. (3) To the measured distance is added 2 cm. to allow for the length of the vein graft investing the cuffs. This computation gives the total length of the vein segment needed. The tension exerted on the inserted vein graft by the normal elastic retraction of the arterial ends decreases the opportunity for pouting and redundancy of the vein graft within the cuffs. Care, of course, must be exercised to install the vein graft in the reverse of its normal axis, allowing the blood to pass any valve that might be in the segment. A functioning valve would doom the procedure.

Extrusion of the prosthesis from the arterial lumen was the reason for failure in Case 2. The causes of this accident are several. First, as noted above, the introduction of this type of prosthesis considerably reduces the area of the arterial lumen, and does so abruptly. Naturally, the blood pressure against this partially obstructing device is great. Added factors, such as pouting of the vein and too small a prosthesis, may increase this hazard. Secondly, the low, rounded ridges on the cuffs may be inadequate to hold the ligature. It would seem preferable if these ridges, while low, could be sharply angulated on the side against which the ligature would rest. Finally, ligation is not sufficiently tight when such an accident occurs. The use of the surgeon's knot, when tying over the inelastic cuff, would seem to be the most dependable procedure.[26]

Mann, *et al.*,[18] report that the internal diameter of an artery may be reduced 70 per cent before there is a 50 per cent reduction in blood flow. What the effects of such a reduction of flow are on coagulation, and on the function of the part, is only conjecture. Thrombosis is a threat in all vascular surgery. The eddying of the stream of blood even around an intima-lined connection probably increases the likelihood of thrombus formation. This would be particularly true when the prosthesis is small. Careless handling of the vein segment and of the arterial ends increases the danger of coagulation. The utmost delicacy must be used in handling these structures. Heparin, or dicoumarol, should be used in all cases.[23, 25] Heparin did not become available to our hospital until the Spring of 1945, and then in only very limited quantities. As a result, only the last two cases in our series had the benefit of the drug. Its use in such a small group cannot be adequately evaluated. Undoubtedly an anticoagulant offers far greater chance of success. Now that the subcutaneous administration of heparin in Pitkin's menstruum has been developed,[25] a great chore has been removed from the postoperative care.

Gas gangrene and hemorrhage, the other principal complications, have been mentioned. Blakemore, and his colleagues, have not been troubled by secondary bleeding. Their technic, as shown by excised specimens, leads to firm union between artery and vein segments.

The time between injury and operation will doubtless seem long to many, but these were the existing conditions. At times the volume of work was overwhelming. During one advance, the time from the patient's admission until he could be operated upon (the "surgical-lag") was 54 hours! None of the cases presented was treated during that time.

The composition of the tube used in Case 7 is not known. It has been suggested that it may have been a polyvinyl acetate plastic. It seems to have been highly satisfactory. The tube was flexible; in hot water it was easily malleable and ridges were moulded on it before its use. The material was almost completely transparent, slightly opalescent.[29] Of course, the conditions for its use were good, for the vessel was incompletely divided and was partially sutured. What if the arterial ends are simply pulled over the ends of the tube and ligated in distraction? Does not the ligature cause necrosis and cut through the vessel wall leading to late hemorrhage? Would this not be particularly to be feared in a gaping wound where the prosthesis had little outside support? Temporary use of such a tube is plausible. That is the way in which Tuffier's tube came to be used in the last war,[3, 4] and the Canadians in this war were using a glass tube in the same way.[19, 29] Perhaps the plastic tube has further possibilities where anticoagulants are used in conjunction. It is quicker and easier to insert, and has not the necessary encroachment upon its lumen by a thickness of vein. Certainly, however, the vein-lined tube is more physiologic, and, when the technical difficulties of insertion are lessened, approaches the ideal alluded to by Leriche and Werquin.[8]

CONCLUSIONS

The nonsuture method offers new hope in the treatment of vascular injuries, and should be attempted when the limb is in danger of ischemic gangrene.

An outline of ideal treatment of a case with a lacerated, divided or thrombosed artery might be as follows:

I. Preoperative:

1. Shock treatment: morphine to allay pain. Papaverine is theoretically good in vascular cases, but not without danger.[24] Transfusions with type specific blood to restore blood volume; this should be controlled by hematocrits, and blood and plasma specific gravity determinations.

2. Prophylactic treatment: antitetanic toxoid or serum with polyvalent gas gangrene serum if the conditions indicate it. Penicillin should be used to counteract wound infection.

3. A sympathetic nerve block should be done on the affected side.

II. Operation:

1. Wide and thorough débridement of the wound.

2. Clean isolation of the vessels involved and temporary local occlusion of the artery with rubber guarded clamps.

3. A cursory examination of the collateral circulation which will give and idea of its ability to support the limb. (See page 3).

4. Preparation of the prosthesis of adequate size from the adjacent vein, being sure to reverse it and to keep one end marked. (Use of a preserved vein transplant would facilitate and speed the procedure.[12])

5. Débridement of the ends of the artery and periarterial stripping one inch away from the divided ends.

6. Removal of all clot from the vessel ends and irrigation of them with a heparin-saline solution.

7. Insertion of the largest-sized prosthesis that can be used, starting the procedure with the upper end of the artery, and releasing the upper clamp to be sure of the flow through the prosthesis.

8. Firm double ligation of the arterial ends over the prosthesis with heavy silk.

9. Release of the occluding clamps.

10. Closure of the vascular sheath and wound whenever possible.

11. Local block of the nerves of the involved limb may prove helpful.

III. Postoperative Care:

1. The blood volume should be kept up with whole blood transfusions as indicated.

2. Penicillin, or chemotherapy,[13] should be continued.

3. The patient should be heparinized by subcutaneous injection of the drug in Pitkin's menstruum.[20, 21, 25] Heparinization includes controlling the coagulation time by adequate measures.

4. Repeated nerve blocks should be given as long as the state of the circulation is in doubt.

5. The extremity should be splinted in a neutral position for ten to 14 days.[6, 9]

6. The limb should be maintained at a subnormal temperature.[22]

SUMMARY

(1) Seven cases with gunshot or shell fragment wounds of major arteries are presented. In all of these vessels a nonsuture anastomosis was attempted with varying results.

(2) A discussion of technical difficulties and possible improvements follows.

(3) The paper is concluded with a plan of ideal treatment of such cases.

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PHENYLPROPANOLAMINE HYDROCHLORIDE:* A VASOPRESSOR DRUG, FOR MAINTAINING BLOOD PRESSURE DURING SPINAL ANESTHESIA

PAUL H. LORHAN, M.D., AND DONN MOSSER, M.D.
KANSAS CITY, KANSAS

FROM THE UNIVERSITY OF KANSAS HOSPITALS, DEPARTMENT OF ANESTHESIOLOGY, KANSAS CITY, KANSAS

THE USE OF PRESSOR AGENTS for the prevention or alleviation of the fall in blood pressure which frequently accompanies spinal anesthesia has become an accepted and very useful practice. A new agent which holds promise of combining in considerable measure the desirable features and minimizing the undesirable properties of these agents, deserves extended clinical evaluation as a potentially very useful agent for this purpose. This is more apparent if one considers briefly the individual pharmacologic characteristics of related compounds.

Whereas epinephrine has the greatest effect on blood pressure of any of these agents; however, its effect is relatively evanescent and is apt to be followed by a short period of hypotension after the pressor response to epinephrine has subsided.

It is particularly noteworthy that with an elevation of the systolic pressure, there is always a decrease in the diastolic pressure and the peripheral vascular resistance.

Epinephrine lacks the property of stimulating the respiratory center and has no appreciable direct effect on the respiratory rate as is seen with ephedrine. When it is given intravenously an apnea may follow due to the reflex inhibition of respiration caused by the increased pressure in the carotid sinus and cardio-aortic area. The pulse rate at the height of the rise is accelerated at first, followed by a bradycardia.

Upon the central nervous system epinephrine has very little stimulating effect. Nevertheless, restlessness, apprehension, headache, and tremor may occur in some individuals.

Epinephrine stimulates the heart by a direct effect on the myocardium and the conduction tissue. In the presence of other factors affecting cardiac irritability, such as cyclopropane or ether anesthesia; epinephrine is particularly likely to precipitate abnormal ventricular rhythms.

Successive administration of the same dose of epinephrine will produce equipressor responses in contrast to repeated doses of ephedrine.

As compared to epinephrine, ephedrine has a relatively low order of

* Phenylpropanolamine hydrochloride is distributed under the name of "Propadrine" hydrochloride; and the material used in this study was provided by the Medical Research Division, Sharp & Dohme, Inc., Philadelphia, Pennsylvania.

pressor activity but the duration of its action is very much longer than that of epinephrine. Its pressor effect is not followed by an hypotension following a single dose, as is seen with epinephrine. Repeated usage of ephedrine at frequent intervals will ultimately produce a myocardial depression. This factor necessitates using it with caution in patients with cardiovascular disease.

Upon the pulse rate a bradycardia usually occurs at the height of the blood pressure response.

Ephedrine stimulates the respiration, whereas epinephrine and neosynephrine usually will produce an "apnea." Ephedrine will increase the respiratory minute volume by approximately 20 per cent.

Upon the central nervous system ephedrine acts as a stimulant and frequently patients under a spinal anesthetic will experience variable degrees of nervousness, palpitation, sweating and marked precordial pain.

Neosynephrine has proved to be a useful drug in sustaining blood pressure. Its pressor effect is greater than that of ephedrine but its duration of action is not as long.

The pharmacologic actions of neosynephrine are similar to those of epinephrine and ephedrine. The blood pressure is raised within a few minutes after injection, reaching a peak and then gradually tapering off to a normal level. Its vasopressor effects last about five times as long as epinephrine and slightly less than ephedrine. It acts principally by peripheral vasoconstriction and slightly by cardiac stimulation. By compensatory reflexes or direct action on the sino-auricular mode it slows the heart rate below normal, so that the ensuing bradycardia may become alarming at times. Accompanying the bradycardia there is a marked dilatation of the heart. Cardiac arrhythmias occur infrequently, and central nervous stimulation is absent.

As will be noted, all three sympathomimetic drugs possess some disadvantages, so that the introduction of a new vasopressor possessing qualities similar to the above agents but with the elimination of the undesirable effects is always welcome.

Phenylpropanolamine hydrochloride was first found by Chen, and his associates,[1] to have a greater pressor effect than ephedrine with the same duration of action. The compound does not possess the action of epinephrine in potentiating cardiac irritability. Unlike ephedrine it does not produce undesirable stimulation of the central nervous system. The properties of prolonged pressor activity unaccompanied by cardiac excitation or a secondary fall in blood pressure without central nervous system stimulation combine to make this a most useful compound. Because phenylpropanolamine hydrochloride offered great promise of overcoming certain disadvantages noted with other agents we have undertaken to evaluate it in a group of 263 patients who have undergone a total of 280 operations (Table I).

Spinal anesthesia was administered for all procedures, novocaine and pontocaine being the anesthetic agents used. The dosages of novocaine ranged from 35 to 120 mg., and of pontocaine from 8 to 20 mg. The level of anesthesia was determined by the type of surgery contemplated, but the eighth

TABLE I

Abdominal Surgery:	
Stomach: (gastrectomy, gastro-enterostomies, gastrostomies, perforations repair)	13
Intestinal: (enterostomy, ileostomy, obstruction)	7
Gallbladder: (cholecystectomy, exploration of ducts, cholecystogastrostomy)	8
Pancreas: (resection of, pancreaticojejunostomy)	2
Appendix: (appendicectomy)	10
Colon: (colostomy, repair of colostomy, resection of, combined abdominal-perineal)	27
Herniae: (ventral, femoral, inguinal, perineal, incisional)	46
Explorations	6
Miscellaneous	10
Total	129
Urologic Surgery:	
Transurethral procedures: (cystoscopy, pyelograms, manipulation of stones)	39
Prostatic resections: (transurethral)	43
(Suprapubic)	14
(Perineal)	5
Bladder: (cystostomy, exploration)	10
Kidney: (nephrectomy, nephrolithotomy)	13
Miscellaneous	9
Total	133
Gynecologic Surgery:	
Hysterectomy: (abdominal, supravaginal, vaginal)	10
Perineorrhaphy	3
Miscellaneous	4
Total	17
Orthopedic Surgery: Total	2

dorsal segment was the usual level for lower abdominal surgery and the fourth dorsal segment for surgical intervention in the upper abdomen. Preoperative medication differed in no way from that customarily administered.

Since it was the object of this investigation to determine the influence of phenylpropanolamine hydrochloride on the blood pressure in the presence of a spinal anesthetic it was necessary to establish the average effective dose of the drug. During early phases of the work, doses as small as 15 mg. were used but were found to be inadequate. After further study with increasing amounts of the drug a consistent and reproducible response was evoked with 50 mg. (1 cc.). The mode of administration by intramuscular injection differed in no way from that employed with similar preparations.

Patients to whom fluids have been administered parenterally either during or after operation were excluded from this study as unsuited to its purpose since such measures would undoubtedly influence blood pressure and render difficult an assessment of the true rôle played by phenylpropanolamine hydrochloride in maintenance of the preoperative blood pressure level.

The time of administration of the drug, as related to the anesthetic agent, is presented in Table II. In the majority of the cases a pressor effect was observed almost immediately following administration, with the blood pressure reaching its maximum response usually within ten minutes.

To evaluate the effectiveness of the drug in maintaining blood pressure it was necessary to establish certain arbitrary criteria. A response was regarded

as "satisfactory" if the systolic pressure did not fall more than 10 per cent below, nor rise more than 25 per cent above, the preoperative level. Such a "satisfactory" response occurred in 263 cases, and in 22 operative cases a fall in blood pressure was noted. It should be observed that nine of these 22 patients had preoperative systolic pressures over 160 millimeters of mercury, and two of the nine received phenylpropanolamine hydrochloride in dosages which, judged by later experience, were inadequate. In the remaining seven

TABLE II

TIME OF ADMINISTRATION OF PHENYLPROPANOLAMINE HYDROCHLORIDE

Prior to administration (by 5–10 mins.)	223
Simultaneously with administration of spinal anesthetic	50
After administration of spinal anesthetic	7
Total	280

TABLE III

AGE DISTRIBUTION

	Male	Female	Total
10–19	5	2	7
20–29	9	10	19
30–39	15	15	30
40–49	13	25	38
50–59	30	10	40
60–69	57	16	73
70–79	46	2	48
80–89	7	0	7
90–99	1	0	1
Total	183	80	263

TABLE IV

PREOPERATIVE BLOOD PRESSURE FINDINGS

Hypertension: (systolic pressure over 160 mm. Hg.)	17 cases
Normal pressure: (systolic pressure from 90–160 mm. Hg.)	243 cases
Hypotension: (systolic pressure below 90 mm. Hg.)	3 cases
Total	263 cases

the preoperative blood pressure level was not maintained though each had received 50 mg. of the drug.

An excessive rise in blood pressure is as undesirable as a fall. An elevation of pressure in excess of 25 per cent of the preoperative systolic level was viewed with disfavor. Such a rise occurred in five patients, in three of which the systolic blood pressure rose above 200 millimeters of mercury. It seems worthy of comment that two of these three patients had initial pressures above 160 millimeters of mercury; in the third, the blood pressure had been normal. Nevertheless, in the majority, phenylpropanolamine hydrochloride controlled the

blood pressure very satisfactorily, maintaining the pressure at the preanesthetic level in 90 per cent of the patients studied.

With respect to age, the patients included in this series ranged from 10 to 95 years, and 49 per cent were over 60 years of age (Table III). The preoperative blood pressure findings, roughly classified, are presented in Table IV. It will be appreciated that the age distribution of the patients necessitated rather liberal interpretation of the significance of preoperative blood pressure readings, so-called "normal" blood pressure being considerably higher for advanced age-groups than the commonly accepted standard.[2] Age also accounts, in large part, for the cardiovascular abnormalities noted in Table V. In view of the lack of homogeneity in this series, and the large proportion drawn from the advanced age-group, it seems fair to say that at least some of the failures with phenylpropanolamine hydrochloride could be explained on the basis of the preëxisting status of the patients treated.

In Table VI the duration of the pressor effect from a 50 mg. dose of phenylpropanolamine hydrochloride has been tabulated in 15-minute intervals,

TBALE V

CARDIOVASCULAR ABNORMALITIES PRESENT PREOPERATIVELY

Cardiac weakness (dyspnea on exertion, pitting edema of ankles)	5
Arteriosclerotic heart disease	12
Arrhythmia	6
Hypertensive heart disease	18
Coronary disease	7
Heart block	2
Cardiac decompensation in the preoperative period	5
Aortic stenosis	1
Rheumatic heart disease	6
Aortic aneurysm	1
Total	63

TABLE VI

DURATION OF PRESSOR RESPONSE WITH A 50-MG. DOSE OF PROPADRINE HYDROCHLORIDE

Time in Minutes	Male	Female	Total
0–15	9	2	11
16–30	33	8	41
31–45	57	11	68
46–60	8	10	18
61–75	5	7	12
			150

from which it is clear that elevation of blood pressure was sustained for as long as 75 minutes after administration, with an average duration of 45 minutes.

The pulse rate remained essentially unchanged, the preoperative rate being maintained in by far the majority of the patients in this series. A slowing of the pulse occurred in 38, and an increase in eight. The criterion on this point was the following: The pulse rate was regarded as unchanged if the rate did not increase or decrease more than 10 per cent of the original rate. In many

cases the character of the pulse, as determined by palpation at the wrist, appeared to be improved.

Eight patients with previously normal heart action developed extra systoles during the preoperative and postoperative periods; pulsus alternans occurred in one of these, and partial heart block in another. A simple tachycardia was observed in 19 instances, some apprehension and nervousness was complained of by three patients, nausea was encountered in three, and cardiac pain in three others. Since 49 per cent of the patients in this series were over 60 years of age and cardiovascular abnormalities were present in 25 per cent, there would appear, prior to treatment, to be no reason to attribute the cause of these developments in the cardiovascular system to the compound. This is especially true since it is extremely difficult to distinguish the possible effects of surgery and of a spinal anesthetic from those produced by phenylpropanolamine hydrochloride. Its use in this series of unselected cases subjected phenylpropanolamine hydrochloride to a relatively severe test in an effort to establish its safety and effectiveness, particularly from the cardiovascular standpoint. The type of surgical procedure carried out, the use of spinal anesthetic agents, and the age distribution of the patients, with practically half in the advanced age group, constituted a combination of factors, each of which has a marked influence upon the cardiovascular status. But even if it is assumed that the vasopressor drug used contributed to all the adverse reactions that occurred, the record of phenylpropanolamine hydrochloride would still be extremely good.

SUMMARY AND CONCLUSIONS

Phenylpropanolamine hydrochloride was used in 263 patients subjected to 280 operations after the administration of a spinal anesthetic. The ability of phenylpropanolamine hydrochloride to maintain blood pressure during the performance of a variety of surgical procedures has been established. The drug is an effective vasopressor agent with a moderately prolonged action—45 minutes—and has no apparent harmful side-effects. The optimal effective dose of phenylpropanolamine hydrochloride was found to be 50 mg. administered intramuscularly, and this dose maintained the blood pressure at preoperative levels in 90 per cent of the patients studied. From our experience with other vasopressor drugs, it would appear that phenylpropanolamine hydrochloride has a vasopressor effect which compares very favorably with the action of epinephrine, ephedrine and neosynephrine and offers certain advantages over them, namely, a more prolonged action without either the sharp rise or fall of blood pressure which usually follows the administration of epinephrine; a more prolonged action than that of neosynephrine, and less frequent excitation, than encountered with ephedrine.

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THE EFFECT OF THE LOCAL REDUCTION OF TEMPERATURE ON SCALD BURNS IN THE RAT*

HAMILTON BAXTER, M.D., AND ROBERT H. MORE, M.D.
MONTREAL, QUEBEC

FROM THE DEPARTMENTS OF SURGERY AND PATHOLOGY, ROYAL VICTORIA HOSPITAL, AND McGILL UNIVERSITY, MONTREAL, QUEBEC

IN SPITE of the increasing interest in hypothermic therapy in a variety of conditions,[1-5] only a few investigators have studied the effects of *local* hypothermia on the healing of thermal burns.[6]

Fay,[7] and Allen, Crossman and Safford[6] state that hypothermia of burned areas results in decreased pain, edema, exudation, infection and tissue damage. They also report that the burns treated by local cooling heal with a pliable scar and without much contracture. Fay does not state the basis for his conclusions but Allen, Crossman and Safford report three cases of thermal burns treated by the local application of ice bags, which were gradually withdrawn during the first week. Their impression was that these burns improved more rapidly than had occurred in their experience when burns were not cooled. In the few cases treated by these investigators, controls were apparently not used. The effect of general cooling in burn and/or traumatic shock has been studied experimentally by Blalock,[8] Sellers and Willard,[9] Elman, *et al.*,[10] and others. Rose[11] has described the clinical application of cooling burned patients by placing them in a tub of water at temperatures of 70°F. On the other hand, so far as we are aware, there are no reports in the literature of experimental work where the effect of the local application of reduced temperatures on thermal burns has been studied over an extended period of time, with the object of examining the effect of hypothermia on the reparative processes. Recently, Large and Heinbecker[12] have reported that the healing of experimental wounds is delayed by local cooling and that the amount of lag is proportional to the length of the cooling period. However, Sano and Smith[13] have shown that under reduced temperatures, fibroblasts in tissue culture formed smaller, more compactly placed cells with less intercellular material than tissue cultures of fibroblasts at 37.5°C. They believed, on the basis of these observations, that granulating surfaces so treated would have finer and less retracted scars. They decided that the optimum temperature was between 25° and 30°C. Nemoto[14] has stated that while maximum growth of fibroblasts cultured *in vitro* occurs at 39°C. the rate diminished with decrease in temperature until no growth occurs at 20°C. Because of these rather conflicting observations, the prevalence of burns in modern warfare, the great variety of therapeutic agents used in their treatment, and the frequently poor cosmetic and functional results obtained in the treatment of burns, especially of the face and limbs, we decided to investigate the effect of prolonged local cooling on the healing of thermal burns in the rat.

* Carried out with the aid of a grant from the National Research Council of Canada under the direction of the Surgical Subcommittee on Shock.

METHODS

Except for preliminary experiments, male hooded rats from the same laboratory colony, five to six months of age, and weighing 300 to 350 Gm., were used. The tail of the rat was burned in the following experiments because among the common laboratory animals the skin of the rat's tail is covered with the least amount of hair. It was thought for this reason that among various experimental animals the reaction of the skin of a rat's tail to a burn might

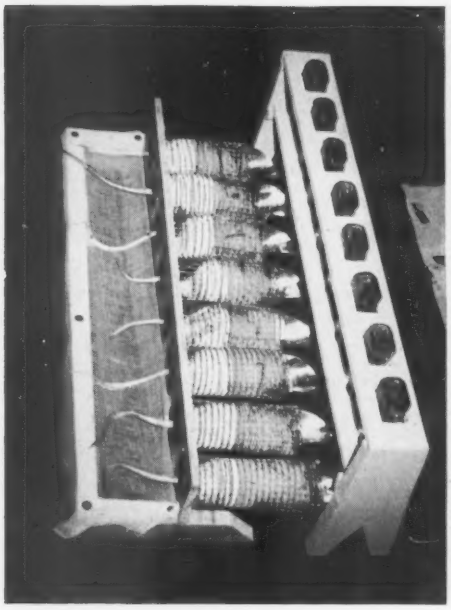

FIG. 1

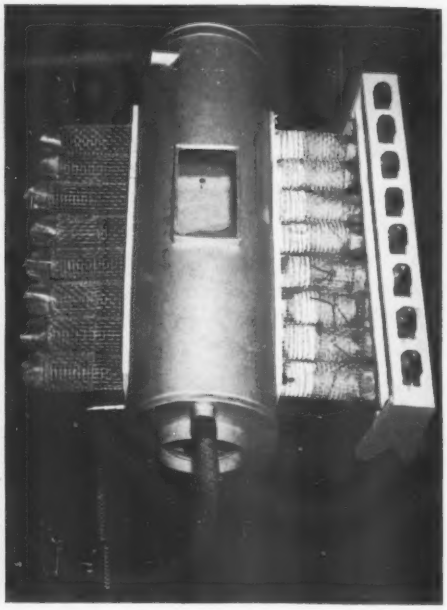

FIG. 2

FIG. 1.—Wire cages arranged to restrain the rats and to prevent them from chewing their tails. The food cups and water bottle rack can be seen. The tails pass through large holes in the board to which the cages are attached. Their tails rest on a gauze tray. This gauze rack is fixed so that the tails are not dependent.

FIG. 2.—Cages similarly arranged to those of Figure 1 but attached to the side of a cooling chamber. The tails pass through large holes in the sides of this chamber and rest on the gauze tray seen through the window.

most closely approximate the reaction of the human skin when it is burned. Preliminary experiments demonstrated that immersion of the rat's tail in water at 100°C. for three seconds consistently produced a moderate degree of tissue damage upon which a reduced temperature might be expected to create some observable effect either beneficial or harmful. For this reason in the following experiments in which a burn was produced the tails were burned for three seconds in water at 100°C. Only the terminals 13 cm. of each tail were burned. This was designated a "standard burn" and will be referred to subsequently as "S. B."

The rats to be burned were anesthetized in an ether chamber for two minutes in a uniform concentration of ether and the tail was then given a S. B.

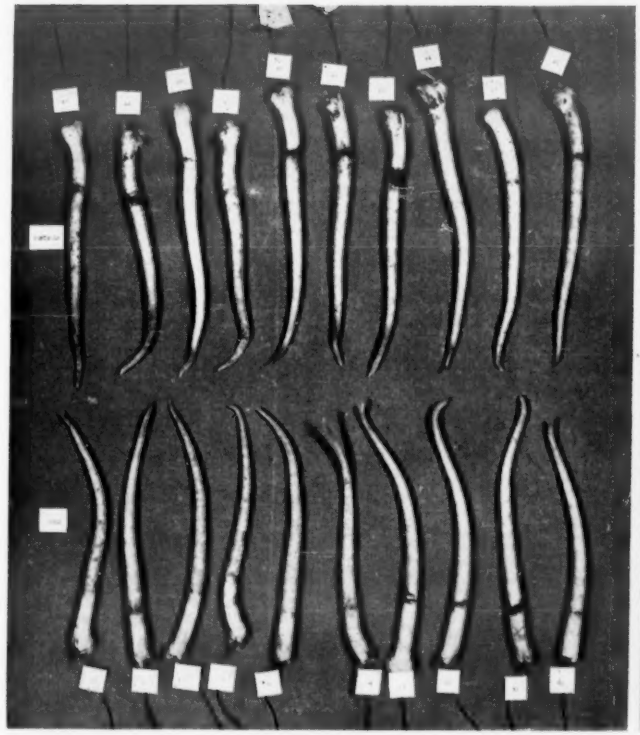

FIG. 3

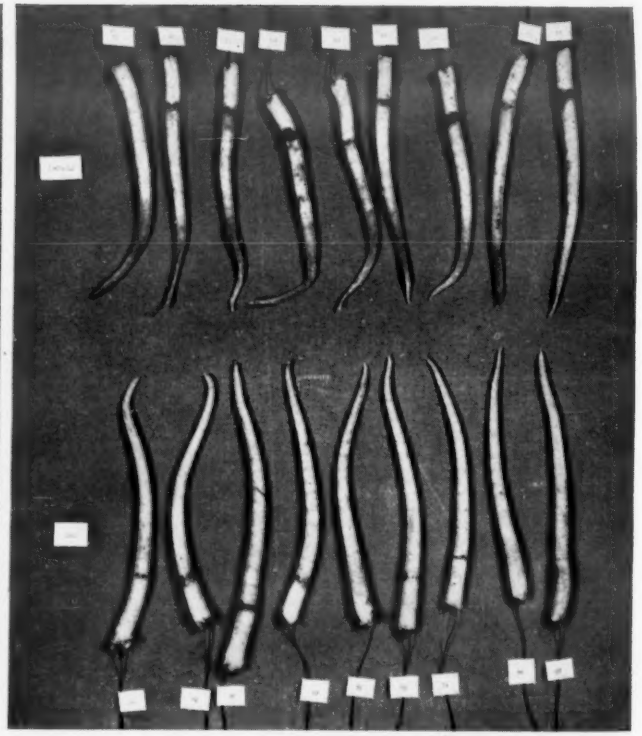

FIG. 4

FIG. 3.—Photograph of tails from Experiment III. All tails given a S.B. Cold group below cooled at 52°F. for eight days. Control group above at room temperature for eight days.

Note the minor terminal shrinking and darkening in the control group due to dry gangrene. Cold group appear normal.

FIG. 4.—Photograph of Experiment IV. All tails given a S.B. Cold group below at 44°F. for 14 days. Controls above at room temperature for 14 days.

Note the definite shrinking and darkening, with twisting of the terminal portion of the control tails. There is very little evidence of gross damage in the cooled tails.

Following the experimental burn and before recovery from the anesthetic, the rats were placed in the cages shown in Figures 1 and 2. The tails of the rats were placed in an insulated metal cylinder (Fig. 2) through which circulated cold air. The temperature of this chamber could be regulated from 36°F. to room temperature and was controlled by a thermostat to within ±2°F. The

FIG. 5.—Photograph of tails from Experiment V. All tails were given a S.B. The tails of the cold group were cooled at 40°F. for 11 days, then gradually brought up to room temperature during the next seven days, and kept at room temperature for ten days. Controls were kept at room temperature for 28 days.

Control tails above show a definite terminal dry gangrene. The cold tails below show a more extensive gangrene which is moist in type. This is associated with swelling and blebbing of all the burned area and, occasionally, slight swelling proximal to the burn.

cold air was prevented from leaking too freely from the chamber and unduly chilling the rats by means of a loose, rubber diaphragm through which the tail was inserted. The hole in the diaphragm was made large enough to accommodate the tail easily so that no mechanical interference with the circulation could occur from constriction. The control rats were placed in similar cages (Fig. 1) but their tails were exposed to room temperature varying from 75° to 80°F. After some experimentation it was found that tape collars attaching

the rats to the anterior part of the cage restrained them most efficiently and interfered least with their well-being and, therefore, prolonged the survival period. Access to as much purina fox chow and water as the rats desired was provided by means of the feeding and watering racks seen in Figures 1 and 2. The hind quarters and proximal part of the tails of the rats were kept clean by allowing the excreta to pass through large holes in the rear of the cages. The tails of all rats surviving for the duration of each experiment and the tails which seemed of interest from rats dying during the experiment were examined grossly and histologically. A daily chart of the appearance of each tail was kept and correlated with the histologic findings. The whole tails were fixed in 10 per cent formalin; blocks were decalcified, embedded in paraffin and sections stained with hematoxylin and eosin. Three transverse sections were taken from each of the tails, one at the proximal end of the burned area, one from the middle of the burned area and one from a point one inch proximal to the tip of the tail. Microscopically, the degree of damage was studied by estimating the amount of separation of the epidermis, the degree of edema, necrosis, hyperemia and cellular inflammatory reaction in the epidermis, dermis, subcutaneous tissue and muscle. The changes were graded as from one plus to four plus according to the amount of damage. Eight experiments in all were carried out and a total of 277 rats were used in these experiments.

EXPERIMENTS AND OBSERVATIONS

Experiment I.—Eight rats were placed in the control cages without burning the tails and kept for 29 days (Fig. 8).

At the end of 29 days the tails of the four survivors appeared normal on gross and microscopic examination.

Experiment II.—Sixteen rats were used in this experiment and none of the tails were burned. The apparently normal tails of these 16 rats were placed in the cooling chamber at 52°F. The tails of eight rats were cooled for seven days and then removed to room temperature. The tails of the remaining eight rats were cooled at 52°F. for a total period of 14 days and then changed to room temperature. At the end of 24 days from the beginning of the experiment all the survivors were killed.

Four animals from each group survived for the duration of the experiment. One tail from the group that was cooled for 14 days presented edema throughout the whole length of the tail which appeared to be due to kinking of the tail early in the experiment. The tails of the seven remaining survivors could not be distinguished in the gross from normal tails. However, microscopic examination revealed a definite though slight shrinking and irregularity of the nuclei of the epidermis, sweat glands and hair follicles. These changes were associated with a minimal loss of the definite outline of the collagen bundles of the dermis. Of more interest was the relaxed and dilated appearance of small and large arteries and veins, associated with a dense packing and clumping of red blood cells within them.

Experiment III.—The tails of 32 rats were given a S.B. The 16 tails of the experimental group were kept at 52°F. for eight days and the 16 tails of the control group were kept at the room temperature for the same period.

Thirteen of the control rats and ten of the experimental rats survived for eight days. A comparison of the appearance of the tails of these rats at the termination of the experiment can be seen in Figure 3. Those of the control group showed a definite dry gangrene of the terminal part of the tails extending for a distance of from one to three centimeters. In the cooled group only a few tails showed minor gross changes at the

tip, while the remainder of the group showed no gross evidence of damage. It was interesting to note during the experiment that the tips of the control tails showed some cyanosis about the 2nd or 3rd day. This condition spread proximally as the distal part became gangrenous. All of the control rats showed a slight swelling of the whole tail for about the first three days, which gradually disappeared as the experiment proceeded.

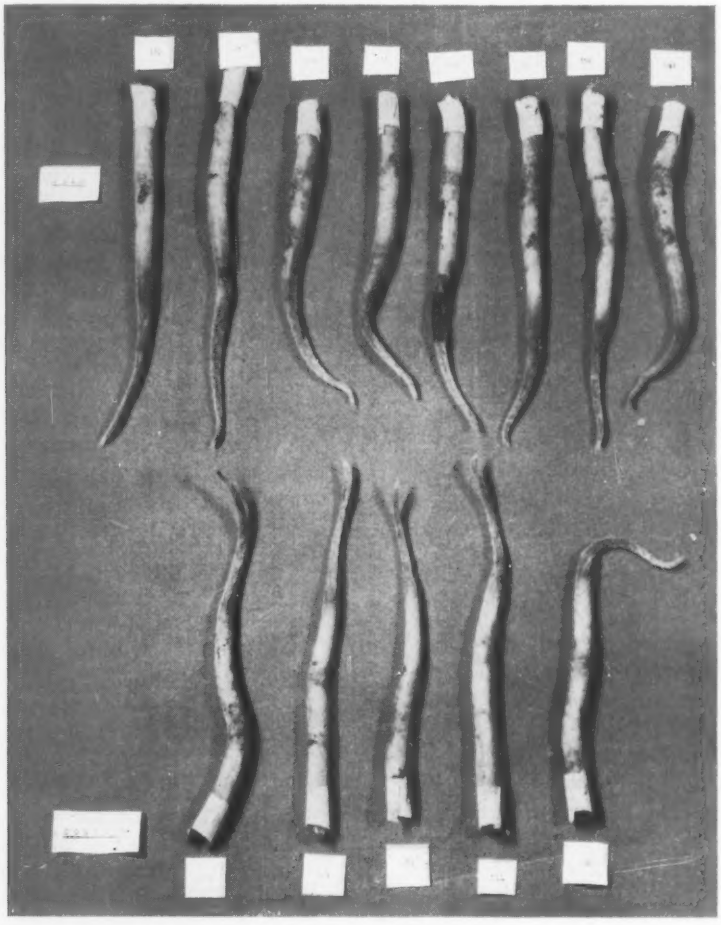

FIG. 6.—Photograph of tails from Experiment VI. All tails were given an S.B. The cooled tails were placed in a temperature of 54°F. for four days, then raised to room temperature during the next six days, and kept at that temperature for eight days. Control tails were kept in room temperature for 18 days.

The control tails below show a definite dry gangrene of the terminal segment. There is more extensive moist gangrene in the experimental group above, associated with swelling and blebbing of all the burned area.

In the experimental group this early swelling never appeared. Many of the experimental tails showed slight cyanosis of the tip about the 3rd day, which then gradually disappeared leaving the tail a normal white color and of soft consistency. The rats with their tails in the cold chamber showed less evidence of painful stimuli following the burns than did the control rats.

The microscopic changes corresponded fairly closely with the gross appearance although the gross changes in the terminal part of the controls were more obvious than the microscopic. Conversely, the microscopic changes in the proximal portion of the tails in both groups were more evident than the gross changes. The terminal part of the control tails presented necrosis of all tissues. In the proximal portions of the tails it is interesting to note that hyperemia was more marked in the cooled tails than in the

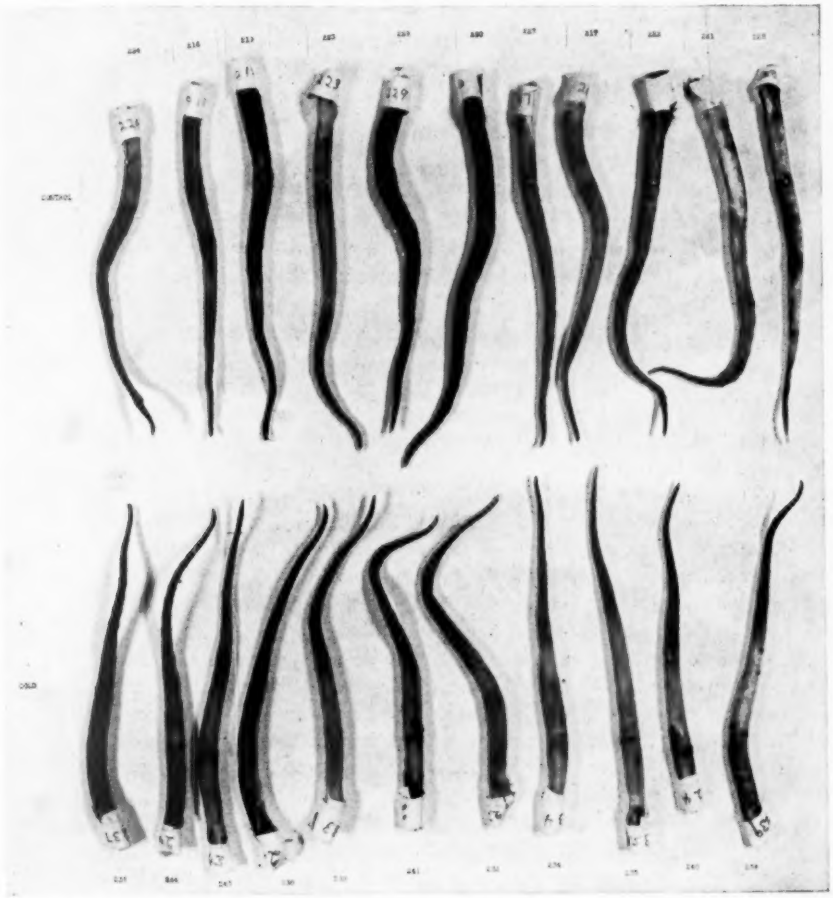

FIG. 7.—Photograph of Experiment VIII. All tails given a S.B. Cooled tails below were kept in a temperature of 63°F. for six days, and then gradually brought up to room temperature during the next five days, and kept in this temperature for 13 days. Control tails above were kept in a temperature of 85°F. for 24 days.

There is a slightly more extensive dry gangrene of the terminal part of the tail than is seen in the control tails.

controls. In the terminal portions of the treated tails the large arteries and veins were dilated, their walls stretched and relaxed, and their lumina often presented marked silting of the red blood cells which appeared to plug the vessels. In the experimental animals the epithelium seemed thicker and less dried out in appearance than that of the controls (Figs. 9 and 10).

Experiment IV.—The tails of 32 rats were given a S.B. The tails of the experimental group were kept at a temperature of approximately 44°F for 14 days. The controls were kept at room temperature.

Nine of the control rats and nine of the treated rats survived for 14 days. The appearance of the tails of these rats at the termination of the experiment is seen in Figure 4. The nine control tails showed changes of a similar nature to those of Experiment III but they were more extensive. The dry gangrene was pronounced and was present in the terminal 2 to 5.5 centimeters. Proximal to this was a cyanotic area and then a band of hyperemia. Two tails of the cooled group presented dry gangrene of the distal centimeter and two other tails showed cyanosis of the distal 4 centimeters but these tails were soft. The remaining five tails of this treated group which survived were white and soft. The time of appearance of the changes in Experiment IV were similar to those of Experiment III. Again the controls showed a generalized swelling of the tails during the first three days following the burn which then disappeared. The cooled tails did not show this early swelling.

The microscopic findings of the 18 survivors paralleled the gross changes. The tails from both groups presented a washed-out appearance in all the soft tissues of the distal half of the tail. In the cooled group nuclear staining was very faint. The epidermis was thicker than in the control group. Again, the most significant microscopic finding in the tails of the treated group was the hyperemia and the silting of red blood cells found in blood vessels of all sizes in many of the tails.

Experiment V.—The tails of 32 rats were given a S.B. The tails of the experimental group were cooled for the first 11 days following the burn in temperatures of 40°F., and then during the next seven days the temperature was gradually brought up to room temperature. The tails were then kept in this temperature for a further ten days, making a total of 28 days for the experiment. The controls were kept at room temperature for the same length of time.

Six of the control rats and four of the treated rats survived for 28 days. The tails of these rats are seen in Figure 5. The tails of the control group showed a dry gangrene of the distal 2.5 to 8 centimeters. One tail was edematous and hyperemic above the dry gangrene to the upper level of the burn. The tails of the four treated surviving rats showed *more* damage than the controls. At the termination of the experiment all of these cooled tails were tremendously swollen from the tip to a centimeter or two above the proximal level of the burn. They were hyperemic and extensive maceration of the skin was present throughout the whole edematous area. It is interesting that all of these tails appeared quite normal for the 11 days that they were maintained at the temperature of 40°F., and the seven days during which the temperature was gradually raised to the room temperature. Furthermore, no gross pathologic changes were noted until approximately four days after the temperature had been maintained at this level. During the following seven days with the treated tails at room temperature, severe damage progressed rapidly with the development of extensive moist gangrene. At the termination of the experiment the moist gangrene of the treated tails produced more damage than was present in the control tails.

Microscopically, nuclei were absent from the skin and subcutaneous tissue of the gangrenous areas of the control tails while in the treated tails nuclear staining was gone throughout the length of the burned area. Polymorphonuclear leukocytes were present in the skin and subcutaneous tissue of the control tails and absent in the treated tails while edema and hyperemia were more prominent in the proximal segments of the treated tails than in the controls.

Experiment VI.—Thirty-two rats were given a S.B. The tails of the cooled group were kept at 54°F. for four days, and then during the next six days the temperature was gradually brought up to room temperature and held for eight days. The total duration of the experiment was 18 days. The control tails were maintained at room temperature for the same period of time.

Five of the control rats and ten of the treated rats survived 18 days. These tails are seen in Figure 6. The tails of the control group showed a dry gangrene of the terminal 5 to 6.5 centimeters while the tails of the treated survivor group showed a moist gangrene

of the terminal 5 to 9 centimeters with occasional blebs proximal to the gangrenous area. Except for a slight terminal cyanosis, all of these tails appeared relatively normal for the four days that the temperature was maintained at 54°F. On the 6th and 7th days this temperature was gradually brought up to 70°F. On the 7th day most of the tails began to show a definite gangrene of the tip which progressed rapidly to an extensive moist gangrene by the 18th day when all of the rats were killed.

FIG. 8

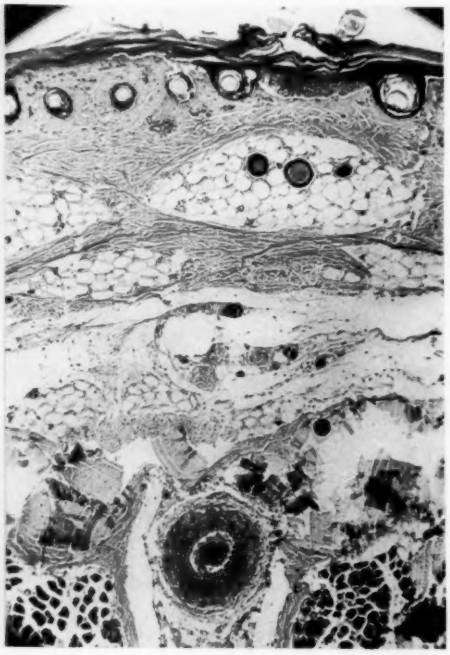

FIG. 9

FIG. 8.—Photomicrograph of normal tail. (Hematoxylin and eosin stain, x 51). Note the moderate thickness of the wall of the caudal artery and the definite outline of muscle fibers in the wall.

FIG. 9.—Photomicrograph of control tail from Experiment III. (Hematoxylin and eosin stain, x 48). Tail given a S.B. and kept at room temperature for eight days. Note the contracted caudal artery in contrast to the experimental tail of Figure 10, from the same experiment.

Microscopically, the necrosis of skin and subcutaneous tissue was slightly more prominent in the controls than the treated tails and there was a good deal of polymorphonuclear infiltration of the skin and subcutaneous tissues of the control tails. Two things of particular interest were present in sections of the treated tails. First, the sections of the terminal part showed a marked dilatation of the large veins which were filled with a brownish homogeneous material composed of laked red blood cells; and, secondly, the large arteries of the more proximal part of the tail were markedly dilated until there was no wrinkling of the internal elastic lamina. Other medium-sized to small veins were dilated and filled with blood. The large arteries of the control tails were extremely contracted.

Experiment VII.—The tails of 24 rats were given a S.B. Of these, eight were cooled at 63°F. for 36 hours. At the end of this period the rats were placed in room temperature. The tails of the 16 control rats were kept at room temperature. The experiment was continued for 18 days at which time the survivors were killed.

Nine of the control animals and four of the group cooled for 36 hours survived until the end of the experiment. It was interesting to observe that the cooled tails developed cyanosis and gangrene very gradually after being removed to room temperature, and were in this temperature usually seven to ten days before very marked changes occurred. However, at the end of the experiment the survivors from the experimental group presented a degree of dry gangrene equal to the control group.

Microscopic examination of sections of the tails of the survivors revealed little difference in the degree of necrosis between the cooled tails and the controls. However, eight hours after scalding the tails of the rats in this experiment, one control and one experimental rat were killed and the effect of eight hours cooling was studied microscopically. Sections of the cooled tail revealed dilatation of blood vessels and silting of red blood cells that was not observed in the control killed at the same time (Figs. 12 and 13).

Experiment VIII.—The tails of 32 rats were given a S.B. Sixteen of the tails were cooled at 63°F. for six days, and then during the next five days the temperature was gradually raised to room temperature and this was maintained for another 13 days. The tails of the remaining 16 rats used as controls were warmed to a temperature of 85°F., in contrast to the usual room temperature of 75°F to 80°F. used for all previous control animals. All survivors were killed on the 24th day of the experiment.

Thirteen of the experimental and 12 of the control animals survived for the duration of the experiment. It was interesting to note that the cooled tails developed some cyanosis of the tip of the tail within 24 to 48 hours of the burning and that this cyanosis persisted and increased. Moreover, within nine days of the burn, while still in the cool box they showed a dry gangrene of the tip. As the temperature was gradually raised to the room temperature, the dry gangrene spread more rapidly. There was a marked increase in the rate of extension of the gangrene about the 3rd day after the cooled tails had been exposed to room temperature. At the termination of the experiment the gangrene was more extensive in the cooled tails than in the control tails (Fig. 7). The tails of the group kept at 85°F. showed a more rapid development of gangrene than in the previous controls kept at room temperature. There were also more blebs proximal to the gangrene than were seen in previous controls.

Microscopic examination of the cooled and uncooled tails revealed only minor difference in the degree of necrosis but there was more edema, vascular dilatation and clumping of red blood cells in the cooled tails.

FIG. 10.—Photomicrograph of experimental tail from Experiment III. (Hematoxylin and eosin, x 83).

Tail given a S.B. and then cooled at 52°F. for eight days. Note the dilated caudal artery and dense packing of red blood cells in the lumina of artery and vein.

FIG. 11.—Photomicrograph from Experiment II. (Hematoxylin and eosin, x 51). Tails not burned, cooled 14 days at 52°F., and then at room temperature for ten days.

Note the dilated caudal artery with thinned-out wall and lumen packed with red blood cells.

FIG. 12.—Photomicrograph of control tail from Experiment VII. (Hematoxylin and eosin stain, x 54).

Tails given a S.B. and kept in room temperature for eight hours. Note the thick muscular wall of the caudal artery.

FIG. 13.—Photomicrograph of cooled tail from Experiment VII. (Hematoxylin and eosin stain, x 51).

Tail given a S.B. and cooled at 63°F. for eight hours and killed immediately on removal from refrigeration chamber.

Note the dilated caudal artery with thinned-out muscle in contrast to that of Figure 12. The lumen is packed with red blood cells.

FIG. 10

FIG. 11

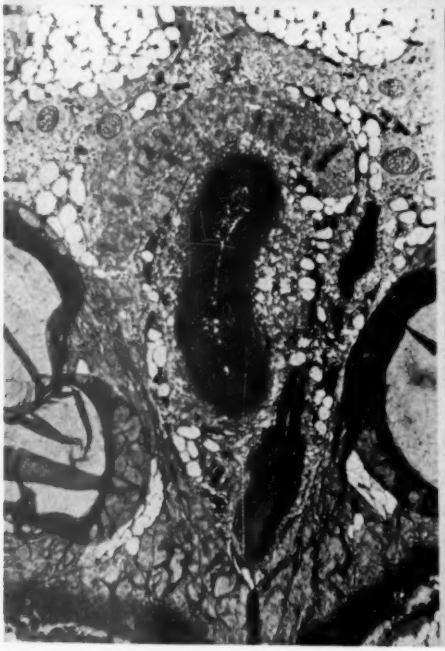

FIG. 12

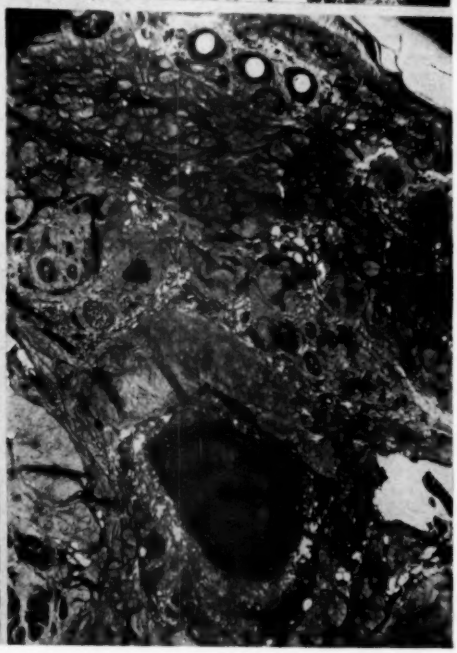

FIG. 13

DISCUSSION.—Many reports have appeared in the literature regarding the beneficial effect of cooling damaged tissues.[15, 16, 17] In view of the relatively superficial nature of the injury in burns it might be anticipated that hypothermia would provide an ideal method of reducing tissue damage and of promoting healing. The results of our experiments on the effect of hypothermia on scald burns of rats' tails indicates that this type of therapy is definitely harmful to the burns under the experimental conditions previously described. Preliminary experiments (Nos. I and II) showed, respectively, that neither the position of the tails in the refrigeration chamber nor the cooling of the *normal* tails, caused any obvious gross pathologic changes although microscopic sections of the cooled tails presented a slight dilatation of blood vessels and hyperemia. While this was not very obvious its appearance suggested some disturbance of circulation due to the cooling. However, an apparently beneficial effect of cooling burned tails was noted grossly when the animals were sacrificed immediately after the period of cooling (Experiments III and IV). In spite of this grossly normal appearance, the microscopic findings of dilatation of blood vessels and the silting of red blood cells indicated that the cooling had affected the circulation of the tails in some way. That the cooling had caused serious damage became apparent when burned tails which had been cooled at a fairly low temperature were allowed to survive for some time at room temperature (Experiment V). Thus, the microscopic changes noted in Experiments III and IV were given time to develop into grossly observable damage. The only constant microscopic change which appeared to be due to the cooling of the tails *per se* was the dilatation of blood vessels and the silting of red blood cells seen in these vessels. Varying degrees of these changes were noted in all tails that were cooled. They were noted in unburned tails cooled at low temperatures for long periods of time, and were also seen in tails cooled at 63°F. for only eight hours. Similar changes were present in the burned tails cooled at identical temperatures and for the same length of time. These alterations persisted for as long as two weeks after the tails were removed to room temperature. These constant findings suggest that they were related to the severe damage noted in the later experiments. In these latter experiments on cooling burned rats' tails the reduced temperatures ranged from 40°F. to 63°F. and were maintained for varying periods of time—from eight hours to two weeks. In all these experiments in which the rats survived for some weeks at room temperature after the period of cooling the treated tails were more severely damaged than the controls. Visible evidence of the damage became marked within a few days after the temperature was elevated and constantly appeared whether it was raised suddenly or gradually to room temperature. In one experiment (No. VIII) the control tails were maintained at a temperature of 85°F., which was approximately 10°F. above the room temperature used for the controls of other experiments. In the controls of this group gangrene developed more rapidly than in the control tails of other experiments. It is interesting to note that the least degree of damage of all the burned tails studied in these experiments was found in the control tails main-

tained at 75°–80°F. and in the cooled tails of Experiment No. VII. In this latter experiment the tails were cooled for 36 hours at 63°F.

These results are contrary to those of other investigators, who have claimed beneficial results in the therapy of burns with cold.[18, 6, 19, 20] Several authors[15, 16, 17] have shown that ischemic tissues can be preserved much longer by early refrigeration than at room temperatures and the evidence on this point is convincing. Allen,[18] Allen, *et al.*,[6] Crossman,[19] and Pickerill,[20] reasoning partly by analogy, have advocated the use of rather low temperatures in the treatment of burns. Although the use of cold may be satisfactory in preserving recently ischemic tissues there seems to be insufficient evidence that it is beneficial in the healing of fresh burns. The clinical evidence supporting the claims of all these authors, so far as we are aware, is based on the impression of only three reported cases.

In view of the fact that our experimental results conflict with the clinical reports of Allen,[18] and others,[6, 19, 20] it is important to investigate the factors which could explain the adverse effects of cold noted in our present study. Recently, there has been a renewed interest in the effect of reduced temperatures on tissues and much experimental evidence has been accumulated that may throw some light on the cause of the damage noted in the rats treated by hypothermia in this present study.

The first important clue to the cause of the harmful effects of cooling burned rats' tails in our experiments was the relaxation and dilatation of the blood vessels associated with the plugging of many of the lumina with red blood cells observed in *burned* and *unburned* tails which had been cooled (Figs. 10, 11 and 13). Greene[21] observed that clumping of red cells and obstruction of dilated vessels were features of the initial reaction to low, dry cold. Ricker[22] decided that this stasis which accompanied chilling of tissue resulted from a vasoparalysis while Tannenberg[23] believed that the mechanism was due to the exudation of serum leaving the vessels packed with red blood cells. Jochim and Hertzman[24] believe that engorgement and damage of the capillary tree occurs because of arteriolar dilatation occurring before the arteriovenous anastomoses open. Grant[25] has shown how these anastomoses respond to local thermic stimuli. All of these authors agree that the final outcome of these phenomena is a plugging of the circulation and consequent anoxia of the tissues.

The next finding of importance was the development of edema leading to extensive moist gangrene in the burned tails which were returned either gradually or suddenly to room temperature after cooling (Figs. 6 and 7). That this edema was not a result of constriction of the tails was proved by Experiment I, where rats with unburned tails were left in the experimental cages for one month without harmful effects. This development of edema is in agreement with Smith, Richie and Dawson,[26] who found that hemorrhage in addition to exudation took place especially after the warming of chilled tissues. Others have noted edema during prolonged cooling[12, 27] which often remained after the temperature had returned to normal.[27] This edema might be due to capillary damage secondary to the vascular dilatation of vessels and plugging

with red blood cells noted by ourselves and others. However, Lewis[28] also believed that cooling of tissues by temperatures of the order used in these experiments and applied for as short a time as two hours, damages the tissues, possibly liberating histamine-like substances which produce hyperemia and edema. Safford and Nathanson[29] suggest that the damage which occurs following a sharp rise in temperature of previously cooled tissue is, in reality, a burn and this results in edema. More recently, degeneration of peripheral nerves has been noted in chilled tissues.[30, 31] Large and Heinbecker[30] suggest that this results in damage to tissues by a loss of normal trophic impulses. It is quite conceivable that this latter observation may be the basis for altered circulation and consequent edema.

Before attempting to draw any general conclusion from these experiments regarding the effect of cooling thermal burns there are a few points that should be mentioned regarding the structure of the tail of the rat which may have operated in producing the results in these experiments, and which might not be operative in other areas of the body. For instance, it is apparent from the controls of our experiments that the scald burns caused sufficient damage to produce a gangrene of all tissues of the distal 6 to 7 centimeters of the tail. For this reason it seems likely that the tail of the rat is sufficiently small that the scald burn used may have penetrated the entire thickness of the distal part of the tail, producing an irreparable degree of damage. It is worth noting, however, that in spite of this irreparable damage the initial cooling did prevent the changes characteristic of necrosis, and these findings agree with Large and Heinbecker who found that the normal response to injury did not appear about incisions made in cooled limbs of dogs. On removal to room temperature severe damage appeared in the burned tails and this observation parallels Large and Heinbecker's finding that their incisions showed an exaggerated response when the cooling was stopped.[12] It is possible that the severe damage which appeared in the cooled tails after elevating the environmental temperature was due to the fact that the skin of the rat's tail provides a thick, unyielding envelope about the tissues, which would increase the obstruction to blood flow resulting from any edema of the enclosed tissues. For this reason it is possible that any harmful effects which the refrigeration may have produced in the tissues and which appeared when the tails were removed to a temperature of 75°F. was exaggerated beyond that which might occur in the cooling of broad surfaces covered with a more delicate skin.

In conclusion, it may be said that the observations in the preceding experiments of this paper indicate that prolonged cooling of only moderate degree induces vasodilatation which is present while the tissues are being cooled and which persist for a long time when the same tissues are again placed in a normal environmental temperature. Greene[21] working with mice at temperatures which produce true frost bite, Lewis[28] working with humans and using temperatures as high as 59°F., and, recently, Friedman[32] in an extensive study of trench foot have all stated that one of the early responses to cold is a vasodilatation. According to Lewis[28] this response is a physiologic defense mechanism

within certain limits. In many of the observations of these workers, the vasodilatation was noted when the tissues were reëxposed to normal temperatures for some time. Our results confirm the views of these investigators and indicate that a permanent vasoparalysis occurs while tissues are being cooled at temperatures as high as 63°F. for a period of eight hours. These results, and the vasodilatation of trench foot[32] and chilblain[28] which occurs in temperatures above that of freezing, make it abundantly clear that a breakdown of the neurocirculatory system can occur in tissues which are cooled, but not frozen.

It is not possible to say whether or not this disturbance of vasomotor control due to cooling was responsible for the poor healing of the burns in the preceding experiments. However, it can be concluded from these results that external temperatures ranging from 40°F. to 63°F. are harmful when applied to a scald burn of the rat's tail. Moreover, it was noted that the lowest temperature resulted in the most severe damage, while a temperature of 63° F. for a relatively short period produced only slightly more damage in the burned tails than occurred in the burned control tails in room temperature of 75°F. Because of the severe burn produced in these experiments and because of the nature of the rat's tail, it would seem unjustifiable to infer that similar treatment of thermal burns in the human would produce analogous results. In view of this, it is interesting to observe that while most of the controls were kept at an environmental temperature of 76°F. the control tails of Experiment No. VIII were kept in a temperature of 85°F. and these latter tails showed more severe damage than the controls kept at 76°F. This finding suggests that the optimum temperature for the treatment of the burns in these experiments was between 65° and 75°F. This coincides with the temperature that Elman, *et al.*[10] found to be associated with the lowest mortality from burn shock in rats and, moreover, these temperatures are relatively cool as compared to the usual temperature to which patients suffering from burns are exposed. These temperatures for the treatment of burns agree with those of Rossiter,[33] and Safford and Nathanson[29] who have recommended the use of temperatures of the order of 70°F. for treatment of burns.

For these reasons it would seem of value to extend these experiments to the human. However, it would be wise in such experiments to commence with temperatures of about 70°F. and proceed with caution as lower temperatures are used, especially when applied to small extremities. Safford and Nathanson[29] reported the treatment of a lesion, possibly a burn, by refrigeration and noted that when the temperature was raised, retrogressive changes occurred until the 89th day of refrigeration. This indicates that refrigeration must be done not only at moderate temperatures but also over a long period of time, and great care must be taken not to raise the temperature too soon nor too suddenly. Moreover, in such treatment of extensive burns, great care should be taken to prevent lowering the general body temperature below normal.

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STREPTOMYCIN IN SURGICAL INFECTIONS: I—LABORATORY STUDIES*

MAJOR EDWIN J. PULASKI, M.C., A.U.S.†
AND
MAJOR HELMUTH SPRINZ, M.C., A.U.S.
WITH THE TECHNICAL ASSISTANCE OF
CARROLL E. HEIST, B.S., AND HELEN B. EHRHORN, B.S.
STATEN ISLAND, N. Y.

FROM THE HALLORAN GENERAL HOSPITAL, STATEN ISLAND, N. Y.

IT IS NOW well established that successful clinical results from antibiotic therapy depend on accurate bacteriologic diagnosis and proven susceptibility *in vitro* of the causal organisms to the chemotherapeutic agent. Research on the clinical effectiveness of streptomycin in certain types of infection afforded the opportunity of making extensive correlative laboratory studies. This communication reports some of the observations and results, including: (1) a broth serial dilution method for testing susceptibility of bacteria to streptomycin; (2) an adaptation of the method for assay of streptomycin in blood and urine; (3) data on absorption, excretion and distribution of the drug in the body; (4) results of susceptibility tests on 1,000 pure cultures of bacteria; (5) comparison of *in vitro* action of streptomycin and penicillin on the gram-positive cocci; (6) a dosage scheme evolved on the basis of the results of bacterial sensitivity tests and drug levels in body fluids; and (7) experiences with drug-fastness and its clinical implications.

1. *Broth Serial Dilution Test.*—The method, briefly, consists in determining the lowest concentration of streptomycin which will produce complete inhibition of growth of the organism to be tested. Wassermann tubes, each containing 2 cc. of a streptomycin standard solution in sterile distilled water, are seeded with 2 cc. of a six-hour broth culture of the organism, diluted 1:50 with broth. The broth employed has the formula, 2 per cent peptone, 1 per cent beef extract, 0.5 per cent sodium chloride, in water, adjusted to pH 7.8.

For routine clinical use we recommend a four-tube set-up, containing aqueous streptomycin standard solutions, of 8, 32, and 256 mcgm./cc.,‡ respectively, and a "water control" in the fourth tube. The addition of the bacterial suspension halves the concentration of streptomycin in the tubes. As a control on each set of determinations, a duplicate test is made, using a *Staphylococcus aureus* "SM" of known susceptibility. After 16 to 18 hours of

* This project was carried out as a part of the study being made under the direction of the Army Medical Research and Development Board, Office of the Surgeon-General.

† Present address: Brooke Army Medical Center, San Antonio, Texas.

‡ 1 mcgm. = 1 "S" unit.

incubation the inhibition is determined by noting the tubes in which no growth has occurred.

2. *Adaptation of Sensitivity Test to Assay of Blood and Urine.*—The sensitivity test has been adapted to the assay of streptomycin in blood and urine. Two cubic centimeters of blood serum is serially diluted with water in the range of 1:1 to 1:32. The same range of dilution is employed for urine, which has been previously diluted with 20 parts of distilled water because of the high concentration of streptomycin usually found in urine. Two-cubic-centimeter amounts of a 1:50 dilution of a six-hour culture of the test organism

TABLE I

BLOOD SERUM AND URINE STREPTOMYCIN LEVELS IN PATIENTS RECEIVING 0.4 GM. DOSES I.M. EVERY 4 HOURS

Case No.	Blood Serum Assay	Urine Assay
15	4–16 Mcgm./cc.	400–1,200 Mlgm./cc.
16	8–16	800–1,200
17	8–16	800–1,200
27†	16–16	2,000+
28*	16–32	64–256
29*	32–32	128–256
40†	16–16	2,000–2,000+
42†	8–16	500–2,000
45†	8–32	500–4,000
53†	8–8	500–2,000
54†	8–16	500–2,000+
59†	4–16	500–2,000

* Marked impairment of renal function.
† Fluid intake restricted to 2,000 cc./24 hrs.

in broth are added to the tubes containing 2 cc. of the serially-diluted body fluid being assayed. Results are read after 16 to 18 hours incubation. Since the growth of the *Staphylococcus aureus* "SM" is influenced by blood sera, we prefer a *K. pneumoniae* strain as the test organism. This bacterium grows luxuriantly in body fluids and gives a sharp end-point.

In assaying the blood and urine for streptomycin, it is important to set-up controls, using patient's blood serum and urine, obtained before the drug is administered. For this purpose 12 cc. of the patient's blood is drawn aseptically and the serum is separated from the clot by centrifugation. Pretreatment urine is collected and Seitz-filtered to render it sterile. Both are refrigerated until needed. Controls are necessary because of variation from day to day in the sensitivity of the test organism in body fluids. Two-tenths cubic centimeter of a 320 mcgm./cc. aqueous solution of streptomycin is mixed with 1.8 cc. of the body fluid in the first of six Wassermann tubes. The contents of this tube are serially diluted with water in the same manner as the test fluid. The concentration of streptomycin in the body fluid tested is then determined by comparing the end-point with that of the control. This assay method is similar to the technics of Donovick, *et al.*,[1] and Price, *et al.*[2]

3. *Absorption, Excretion and Distribution.*—Our data on the absorption and excretion of streptomycin are in substantial agreement with the findings of other workers.[3,4,5,6,7] After intramuscular injection, which is the route of

choice, effective blood levels are rapidly produced. The maximum concentration is achieved within 30 minutes and lasts for about three hours, though high levels are still noted at four hours, and even after this period assayable streptomycin can be detected in the blood. Streptomycin is rapidly excreted in the urine, and, after oral administration, in the feces, but the rate is slower than the rate reported for penicillin. Typical levels maintained in the blood and achieved in the urine, following the intramuscular administration of 0.4 Gm. streptomycin in 4 cc. of physiologic saline every four hours, are presented in Table I.

It will be noted that the dosage used is sufficient to maintain a serum concentration of 4 to 32 mcgm./cc. in the blood serum, with a mean of 16 mcgm./cc. In urine, on an average fluid intake of 2,500 to 3,000 cc. per day, the streptomycin level varies from 400 to 1,200 mcgm. per cc. If the fluid intake is restricted, these levels may be doubled. On the contrary, if renal function is impaired, low urine levels and high blood serum levels are obtained.

The distribution of streptomycin in the body was determined in three cases in which death occurred during the course of treatment. Representative slices of various organs were ground, and the streptomycin was extracted with isotonic saline solution. In addition, assays were made on blood and bile obtained after death. The findings, briefly, are as follows:

(a) Streptomycin was recovered from the bile in one-quarter the concentration present in blood serum. Similar results were obtained on assay of simultaneous samplings of blood serum and bile draining through choledochostomy tubes in two patients.

(b) Pericardial fluid, pleural transudate and ascitic fluid contain one-quarter to one-half of the blood serum level. Studies on patients with ascites suggest that the streptomycin level achieved with a given dosage in the peritoneal fluid depends on the amount of dilution. Streptomycin does not diffuse readily from the blood stream into cerebrospinal fluid. Direct injections are necessary to achieve therapeutic concentrations.

(c) The kidney, liver, muscle and thyroid yield clinically significant amounts of streptomycin, while no assayable streptomycin is found in lymph nodes, spleen, testis, brain and lung parenchyma. Traces only are detected in the prostate and pancreas. Prostatic fluid obtained from six living subjects under treatment with streptomycin contained none of the drug. The findings seem to explain our failures in the treatment of chronic lesions of the prostate due to susceptible organisms, even with relatively large doses of streptomycin administered parenterally.

Pus obtained from thick-walled soft-tissue abscesses was tested for streptomycin in four cases, all with negative results. From these findings it is reasonable to assume that the parenteral administration of streptomycin, like the parenteral administration of other drugs, will neither sterilize abscesses nor cause them to disappear. Streptomycin activity is not influenced by pus, except mechanically.

4. *Susceptibility of Bacteria to Streptomycin.*—The mean blood serum level of 16 mcgm. per cc. which is maintained by the intramuscular administra-

tion of 0.4 Gm. streptomycin every four hours, is the basis for the classification of gram-negative bacteria, as follows:

Inhibition by 4 mcgm./cc. streptomycin—Very sensitive.

Inhibition by 16 mcgm./cc. streptomycin—Sensitive.

TABLE II

ANTIBACTERIAL ACTION OF STREPTOMYCIN: GRAM-NEGATIVE ORGANISMS

Organisms and Total Number of Strains		Streptomycin Mcgm./Cc.*								
		0.5	1	2	4	8	16	32	64	128
Aerobacter aerogenes	(53)	..	3	10	14	10	5	2	4	5
Alcaligenes fecalis	(1)	..	..	1	..	..	..	..	..	...
Brucella melitensis†	(9)	5	2	1	..	..	..	..	..	1
Chromobacterium indicum	(1)	..	..	..	..	1	..	..	..	...
Chromobacterium violaceum	(1)	..	..	..	1	..	..	..	..	...
Eberthella pyogenes	(1)	..	..	..	..	1	..	..	..	...
Eberthella typhosa	(12)	..	2	2	4	3	1	..	..	...
Escherichia coli	(60)	..	2	11	16	19	7	4	..	1
Hemophilus influenzae†	(3)	..	1	2	..	..	..	..	..	...
Paracolon group	(32)	..	..	7	6	11	6	..	1	1
Klebsiella pneumoniae, Type–A	(28)	..	2	9	11	4	..	1	..	1
Klebsiella pneumoniae, Type–B	(23)	..	..	10	5	3	..	..	..	5
Klebsiella pneumoniae, no type	(19)	..	2	4	4	5	2	..	1	1
Neisseria catarrhalis	(4)	..	2	1	1	..	..	..	..	...
Pasteurella avicida†	(2)	..	..	2	..	..	..	..	..	...
Pasteurella boviseptica†	(1)	..	..	1	..	..	..	..	..	...
Pasteurella equiseptica†	(1)	..	1	..	..	..	..	..	..	...
Pasteurella oviseptica†	(2)	..	..	2	..	..	..	..	..	...
Pasteurella pestis†	(2)	2	..	..	..	..	..	..	..	...
Pasteurella suilla†	(1)	..	..	1	..	..	..	..	..	...
Proteus mirabilis	(1)	..	..	..	..	..	..	..	1	...
Proteus morganii	(57)	..	1	2	7	20	7	4	5	11
Proteus vulgaris	(121)	..	..	8	13	55	32	7	4	2
Pseudomonas aeruginosa	(98)	..	..	2	5	29	33	10	4	15
Salmonella aertrycke	(1)	..	..	..	..	..	..	1	..	...
Salmonella enteritidis	(3)	..	..	..	..	2	..	1	..	...
Salmonella para A	(4)	..	..	..	1	3	..	..	..	...
Salmonella para B	(5)	..	..	..	..	2	1	2	..	...
Salmonella pullorum	(2)	..	..	..	2	..	..	..	..	...
Salmonella typhimurium	(1)	..	..	..	..	..	1	..	..	...
Serratia marcescens	(2)	..	..	..	1	..	..	..	1	...
Shigella dysenteriae Shiga	(3)	..	..	1	..	2	..	..	..	...
Shigella paradysenteriae	(5)	..	..	..	4	1	..	..	..	...
Total	(559)	7	18	77	95	171	95	32	21	43

* One microgram = 1 "S" unit.

† Test broth enriched with blood.

No inhibition by 16 mcgm./cc. streptomycin—Insensitive.

No inhibition by 128 mcgm./cc. streptomycin—Resistant.

This classification also applies to infections involving the genito-urinary tract despite the fact that streptomycin is excreted in high concentrations in the urine.[8] Experience with the treatment of over 350 cases of urinary tract infections has shown that bacteria which grow in a concentration of 16 mcgm./cc. are rarely eradicated from the urine.

Tables II and III present the *in vitro* sensitivities to streptomycin of 550 gram-negative and 452 gram-positive bacteria. Eight hundred forty-six

cultures were isolated from infections observed in the course of this study, and 165 were from a stock culture collection of bacteria.* Our studies showed that the over-all susceptibilities were the same for bacteria freshly isolated from human sources and for bacteria cultivated on artificial media for prolonged periods of time. For this reason they are listed together. These tests, in general, indicate that:

TABLE III

ANTIBACTERIAL ACTION OF STREPTOMYCIN: GRAM-POSITIVE ORGANISMS

Organism and Total Number of Strains		Streptomycin Mcgm./Cc.* 0.5	1	2	4	8	16	32	64	128
Bacillus anthracis	(4)	4	..	..	..	.	..	..	..	...
Bacillus cereus	(1)	.	..	1	..	..	..	..	..	...
Bacillus megatherium	(1)	..	..	..	1	..	..	..	..	...
Bacillus mesentericus	(1)	..	1	..	..	..	..	..	..	...
Bacillus mycoides	(4)	..	..	2	1	1	..	..	..	...
Bacillus novus	(1)	1	..	..	..	..	..	..	..	...
Bacillus subtilis	(10)	1	2	1	..	4	..	..	..	2
Corynebacterium diphtheriae†	(2)	..	..	1	1	..	..	..	..	...
Diphtheroid bacilli	(73)	25	9	8	2	1	..	2	1	25
Diplococcus pneumoniae†	(10)	..	..	7	2	1	..	..	..	...
Micrococci	(5)	3	2	..	..	..	..	..	..	...
Staphylococcus albus	(6)	2	..	2	1	..	..	..	..	1
Staphylococcus aureus, hemolytic	(150)	43	31	11	18	8	5	5	2	27
Staphylococcus aureus, nonhemolytic	(12)	6	2	1	..	..	..	..	..	3
Streptococcus hemolytic†	(36)	1	4	2	10	9	5	1	4	...
Streptococcus nonhemolytic	(73)	9	1	3	15	5	25	6	..	9
Streptococcus viridans	(63)	7	4	3	5	14	13	9	1	7
Total	(452)	102	56	42	56	43	48	23	8	74

* One microgram = 1 "S" unit.
† Test broth enriched with blood.

(a) Streptomycin effectively inhibits the growth of a wide variety of aerobic gram-negative and gram-positive microorganisms. However, the range of sensitivity in both groups is wide, and considerable within species variation is a common feature. The practical need for routine determinations of susceptibility of bacteria in conjunction with therapy is apparent.

(b) Most strains of *Brucella melitensis, Eberthella typhosa, Escherichia coli, Hemophilus influenzae, Klebsiella pneumoniae* Type-A, *Pasteurella,* and *Shigella, dysenteriae* and *paradysenteriae,* are inhibited by 16 mcgm./cc. of streptomycin.

(c) Resistant strains of bacteria are frequently encountered among *Aerobacter aerogenes, Klebsiella pneumoniae* Type-B, *Proteus* and *Pseudomonas.* It may be assumed that resistant members will be found in all groups when large numbers of strains have been checked.

(d) Most aerobic sporulating gram-positive rods are very sensitive to streptomycin. Attention is directed to *B. anthracis,* four different strains having been found inhibited by 0.5 mcgm. of streptomycin per cc.

* Obtained through the courtesy of Dr. H. E. Morton, University of Pennsylvania School of Medicine.

(e) Diphtheria bacilli are sensitive to streptomycin, while Diphtheroids may be very sensitive or highly resistant.

(f) Pneumococci are uniformly inhibited, regardless of serologic type. There is little difference in susceptibility between "S" (smooth) and "M" (mucoid) colony forms.

(g) Staphylococci and streptococci exhibit a wide variation in sensitivity. Staphylococci show no distinction in their susceptibility to streptomycin irrespective of their coagulase or hemolytic properties. Streptococci in their susceptibility to streptomycin show no distinction as relates to their red cell reaction, or the serologic grouping of the hemolytic variety.

SUSCEPTIBILITY OF CLOSTRIDIA AND FUNGI

Not listed in the tables are results of tests on the following *Clostridia,* which were grown in media rich in reducing substances (thioglycollate, brain-heart infusion) : *Cl. botulinum,* Types-A and B, *Cl. butyricum, Cl. histolyticum, Cl. novyi, Cl. putrificum, Cl. septicum, Cl. sporogenes, Cl. welchii,* and *Cl. tetani.* All were found insensitive. In addition, two strains each of the fungi, *Candida albicans* and *Saccharomyces cereviseiae,* grew uninhibited in the presence of 128 mcgm. per cc. of streptomycin.

EFFECT OF BLOOD ON SUSCEPTIBILITY OF GRAM-POSITIVE COCCI

It was observed that the *staphylococcus* "SM" strain, which is inhibited by 0.5 mcgm. per cc. streptomycin in the test broth, requires 4 mcgm. per cc. when blood is added. Table IV compares the *in vitro* action of gram-positive

TABLE IV

COMPARISON OF STREPTOMYCIN SENSITIVITY IN PLAIN, MODIFIED AND BLOOD-ENRICHED MODIFIED F.D.A. BROTH

Organism	F.D.A.	F.D.A. 3% Blood
B. subtilis	<0.5	1
B. anthracis	<0.5	<0.5
B. anthracis	<0.5	1
Staph. aureus	2	8
Staph. aureus "SM"	0.5	4
Strep. gamma	8	64
Strep. gamma	8	64
Aerogenes-Fried	64	64
Proteus vulgaris	4	8
E. coli	8	4
Ps. aeruginosa	64	64
E. typhosa	2	2

and gram-negative bacteria in the test broth with the same medium containing 3 per cent citrated human blood. It will be noted that the effect of streptomycin on gram-positive cocci is reduced four to eight times in the presence of blood, while the inhibition of gram-negative and gram-positive bacilli is unaltered. Identical results are obtained if 10 per cent human serum or plasma is substituted for whole blood. For this reason, we consider these organisms susceptible only when they are inhibited in the test broth by 4 mcgm./cc. of streptomycin, or in blood enriched broth by 16 mcgm./cc. of streptomycin.

5. *Comparison of In Vitro Action of Streptomycin and Penicillin on Gram-positive Cocci.* The results of a comparative study of the susceptibility of 250 cultures of gram-positive cocci to both penicillin and streptomycin are presented in Table V. The high incidence of penicillin refractory strains of gram-positive cocci* emphasizes the need for an alternative chemotherapeutic agent.

TABLE V

COMPARISON OF IN VITRO ACTION OF STREPTOMYCIN AND PENICILLIN ON GRAM-POSITIVE COCCI

Organism and Number of Strains		Penicillin Sensitivity Oxford U/Cc.	Streptomycin Sensitivity Mcgm./Cc.* 0.5	1.0	2.0	4	8	16	32	64	128+
Staph. albus.....	(3)	0.156	1	..	..	..	..	..	..	..	2
Staph. albus.....	(3)	>2.5	..	..	..	1	..	..	..	..	2
Staph. aureus, nonhem...	(3)	0.078	2	..	1	..	..	..	..	..	..
Staph. aureus, nonhem...	(2)	0.156	1	1	..	..	..	..	..	..	..
Staph. aureus, nonhem...	(1)	0.312	..	..	..	..	..	..	..	..	1
Staph. aureus, nonhem...	(1)	0.625	..	1	..	..	..	..	..	..	..
Staph. aureus, nonhem...	(11)	>2.5	5	4	..	..	..	..	..	..	2
Staph. aureus, hemolytic.	(1)	0.019	..	1	..	..	..	..	..	..	..
Staph. aureus, hemolytic.	(2)	0.039	1	1	..	..	..	..	..	..	..
Staph. aureus, hemolytic.	(3)	0.078	1	2	..	..	..	..	..	..	..
Staph. aureus, hemolytic.	(7)	0.156	3	2	1	..	1	..	..	..	..
Staph. aureus, hemolytic.	(3)	0.312	1	2	..	..	..	..	..	..	..
Staph. aureus, hemolytic.	(2)	0.624	..	..	..	..	2	..	..	..	..
Staph. aureus, hemolytic.	(3)	1.25	..	2	..	..	1	..	..	..	..
Staph. aureus, hemolytic.	(2)	2.50	..	..	..	..	..	..	..	..	2
Staph. aureus, hemolytic.	(103)	>2.5	24	22	14	16	4	3	1	1	18
Strep. viridans, alpha....	(5)	0.078	..	1	..	..	..	3	..	..	1
Strep. viridans, alpha...	(1)	0.156	..	..	..	..	..	..	1	..	..
Strep. viridans, alpha....	(1)	0.312	1	..	..	..	..	..	..	..	.
Strep. viridans, alpha....	(1)	0.625	1	..	..	..	..	..	..	..	..
Strep. viridans, alpha....	(7)	0.125	1	..	..	3	1	1	..	..	1
Strep. viridans, alpha....	(47)	>2.5	3	2	2	4	11	10	9	..	6
Strep. hem., beta.....	(1)	0.009	..	..	..	..	..	1	..	..	..
Strep. hem., beta.....	(1)	0.156	..	1	..	..	..	..	..	..	..
Strep. hem., beta.....	(2)	0.039	..	..	..	..	2	..	..	..	..
Strep. hem., beta.....	(1)	0.625	..	..	..	..	..	..	1	..	..
Strep. hem., beta.....	(2)	0.125	..	..	..	..	1	..	..	1	..
Strep. hem., beta.....	(12)	>2.5	..	1	..	2	4	3	..	..	2
Strep. nonhem.-gamma..	(3)	0.625	..	..	..	..	1	1	1	..	..
Strep. nonhem.-gamma..	(1)	2.5	..	..	..	1	..	..	..	..	..
Strep. nonhem.-gamma..	(15)	>2.5	..	..	1	1	1	6	3	..	3
Total.....	(250)	.....	45	43	19	28	29	28	16	2	40

* One mcgm. =1 "S" unit.

It will be noted that, generally, penicillin indifferent cocci are streptomycin-sensitive, and *vice versa.* Twenty-nine of 119 strains of staphylococci (24 per cent) were resistant to both antibiotics. Twenty-three of 74 strains of streptococci (31 per cent) were likewise resistant to both antibiotics. The remaining organisms were mutually susceptible. The findings of a 76 per cent susceptibility rate of penicillin-resistant staphylococci to streptomycin, and a 69 per cent susceptibility rate of penicillin-resistant streptococci to streptomycin, strongly favor a therapeutic trial of streptomycin, if warranted by the clinical and labo-

* These were isolated from patients on prolonged courses of penicillin.

ratory findings. We have demonstrated that subinhibitory amounts of streptomycin and penicillin combined are cumulative in effect. There may be an advantage to administering both drugs simultaneously in selected cases.

6. *Dosage.* As the result of our correlative studies of the clinical and laboratory properties of streptomycin, the following principles have been evolved for determining dosage schedules:

(1) Infections due to bacteria which grow uninhibited in the presence of 16 mcgm./cc. of streptomycin are usually not influenced, regardless of the amount of drug administered.

(2) Doses of 0.5 Gm. of streptomycin administered intramuscularly every four hours maintain blood serum levels in excess of 16 mcgm./cc.

(3) There is no evidence that additional benefits accrue from doses in excess of 3 Gm. a day parenterally administered, regardless of the type and severity of infection.*

(4) The severity of untoward reactions is related to the size of the dose and the duration of therapy.

(5) The anatomic location of the lesion, and the concentration of streptomycin attainable at the site, govern the dosage and mode of administration.

Parenteral Administration.—In the treatment of infections including bacteriemia, pneumonia, peritonitis, and acute cellulitis, 3 Gm. per day, in divided doses, is adequate, provided the organisms are susceptible *in vitro,* and adequate levels can be reached in the affected tissue. Two grams per day are usually sufficient in the treatment of infections of the urinary tract, and of specific infections, such as tularemia. Regardless of dosage, adequate drug levels are not possible in poorly vascularized tissues.

Local Administration.—Local administration of streptomycin is necessary in the treatment of infections of the ear, meninges, brain, pleura, and tracheobronchial tree. The dosage employed varies from 50 to 250 mg., dissolved in an appropriate amount of sterile isotonic saline.

Oral Administration.—Oral administration is required for the treatment of intra-enteric infections. A dosage of 1 Gm. every eight hours, in water, is optimum.

7. *Drug-fastness.*—Bacteria rapidly acquire habituation to doses of streptomycin which were originally lethal. This phenomenon is most commonly observed during the treatment of urinary infections, and occurs either when sublethal doses of the drug are employed or with lethal concentrations of the drug in the presence of nonsterilizable foci of infections. The development of drug-fastness may be extraordinarily rapid, occurring in the urinary tract with as little as two days of therapy. Once it occurs, drug-fastness is irreversible, and drug-fast bacteria reproduce drug-fast bacteria. The change is specific and does not indicate concomitant resistance to other chemotherapeutic agents. Table V showed most streptomycin-resistant strains of gram-positive cocci are susceptible to penicillin and *vice versa.* The two agents may be used simul-

* This statement is based on accumulated experience with 1,000 streptomycin-treated cases of infection in U. S. Army Hospitals.

taneously if the clinical course of the disease warrants. One agent can be substituted for the other if maximum effects are not achieved within a few days by the one first employed.

SUMMARY

1. One thousand cultures of bacteria were tested for their susceptibility to streptomycin by a broth-serial-dilution method. The results are tabulated.

2. Data are presented on results of studies on absorption, distribution, and excretion of streptomycin in the body following parenteral administration of the drug.

3. The results of susceptibility tests and of assays of blood serum concentrations of streptomycin have been correlated. On this basis a division between clinically-sensitive and clinically-refractory bacteria is made.

4. The *in vitro* action of streptomycin and penicillin on 250 strains of gram-positive cocci is compared.

5. The principles which govern dosage are outlined.

6. Certain data on drug-fastness are presented.

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SYMPATHECTOMY IN TRENCH FOOT

LT. COL. HARRIS B. SHUMACKER, JR., M.C.,
NEW HAVEN, CONN.

AND

MAJOR DAVID I. ABRAMSON, M.C.
CHICAGO, ILL.

FROM THE VASCULAR CENTER, MAYO GENERAL HOSPITAL, GALESBURG, ILLINOIS.

TRENCH FOOT is a syndrome which follows prolonged exposure of the feet to a wet and cold environment. In contrast to frostbite, it often occurs in weather which is not freezing. The moisture of the shoes and socks renders the limb more susceptible to thermal injury, since it reduces or eliminates the phenomenon of supercooling in tissues.[1] Moisture also facilitates heat loss from the foot and more effective transmission of cold to the body. The initial response of the blood vessels in the limb to such environmental conditions is marked vasoconstriction, and, as this persists, the resistance of the tissues to the trauma of cold diminishes. The cramped position in the slit-trench or other emplacement and the absence of muscular movements also contribute to the decrease in circulation.

The physiologic and pathologic alterations in the foot may result in actual necrosis of tissue, or, if this does not occur, there may still be loss of nails, the production of vesicles, or desquamation of skin. Even in the absence of gangrene, extensive damage to muscles and nerves may take place, followed by fibrosis, atrophy, contractures, sensory disturbances, and pain on weight-bearing. The intense vasospasm observed initially may be replaced by a transient period of hyperemia, and subsequently, in most instances, by the return and persistence of excessive sympathetic tonus.

Since vasoconstriction is, therefore, one of the fundamental factors in the pathogenesis of trench foot and also one of the most common sequelae, it is important to inquire into the therapeutic effect of such a procedure as sympathectomy, which is capable of completely eliminating the hypertonus. It is the purpose of this communication to present the data obtained following the use of lumbar sympathectomy in the treatment of trench foot and to discuss its applicability and limitations.

USE OF SYMPATHECTOMY IN THE EARLY TREATMENT OF TRENCH FOOT

Little information is available concerning the use of lumbar sympathectomy in the treatment of the early stage of trench foot. Edwards, and his associates[2] have studied the problem in 13 patients and have come to the conclusion that the results are good in those individuals with gangrene, but that the procedure did not help those with tender, painful, aching feet of the swollen, warm, and nonswollen types.

We have had no personal experience with this problem, but have had the opportunity subsequently to observe two patients in whom this procedure was performed during the first few weeks after exposure. One of these was con-

vinced that the operation had aided in healing his gangrenous toes, although when he was seen by us eight months later, two tiny ulcers had recurred which healed readily with warm compresses. The second patient had undergone a left lumbar sympathectomy 30 days after exposure, and this had resulted in a warm, dry foot, with some decrease in edema but no effect upon the pain.

SYMPATHECTOMY IN THE LATER TREATMENT OF TRENCH FOOT

Approximately 700 patients with trench foot were admitted to the Vascular Center at the Mayo General Hospital during the period from June, 1944, to October, 1945, and of this number, 49 were subjected to sympathectomy. In all, 66 lower extremities were sympathectomized. In every instance, under spinal anesthesia, the second and third lumbar sympathetic ganglia with the intervening chain were excised through an anterior extraperitoneal approach. No complications occurred. In many patients the operation was preceded by a procaine lumbar sympathetic block, in order to obtain some information as to the possible effects of sympathetic denervation on the clinical manifestations. The results with this procedure were utilized in making a decision as to whether or not sympathectomy would be of any therapeutic value.

The following data have been segregated into three groups according to the chief indication for operation; namely, (1) the presence of extensive gangrene; (2) the existence of excessive sympathetic tonus; and (3) the complaint of pain on weight-bearing. In addition, the effect of sympathectomy on the neurologic and certain other manifestations of trench foot has been evaluated in a separate section.

PATIENTS WITH DEEP GANGRENE

Thirty patients in the series had deep gangrene, and in all, 38 lumbar sympathectomies were performed upon them. The operation was done within one to two months after exposure in the case of 16 individuals, two to three months in ten, and 3.5 to eight months in the remaining four (Table I).

Infection was present in all cases except one, while in 26 individuals there was obvious evidence of excessive sympathetic tonus, with coldness, cyanosis, and hyperhidrosis. These findings were sometimes masked by the local heat resulting from the associated infection. In 16 extremities complete gangrene of one to five toes was present while in 35, portions of toes were involved. In 13 limbs removal of the gangrenous tissue left the heads of one, or more, metatarsal bones exposed. Five of the patients had ulcers of the heel or foot. All but three were bedridden when admitted to the hospital.

Generally, at the same time that the sympathectomy was performed the gangrenous parts were amputated through the line of demarcation, and subsequently débridement, revision of stumps, small deep, split-thickness and tube-transfer grafts were carried out, as indicated in Table I. In only one instance (Case 2) was it feasible to perform an amputation with primary closure. In all other patients, infection presented a difficult problem, not because of its spread into adjacent soft tissues but because it interfered with skin grafting or had produced osteomyelitis of the stumps. In most instances the

infection was mixed in type. Among the organisms found were various sulfonamide- and penicillin-sensitive bacteria but frequently also resistant *B. proteus* and *B. pyocyaneus*. As a general rule, sulfadiazine or penicillin was given on admission, and all patients were treated with warm sterile saline compresses applied locally.

Results.—Following sympathectomy the infection generally cleared up rapidly, and satisfactory healing occurred in all cases. In those instances in which the metatarsal bones were exposed and skin grafts were necessary, the period for complete healing was increased. The average duration of hospitalization after sympathectomy was 4.5 months, but this gives no index as to the rate of healing, since a sick leave of three or four weeks and a regimen of reconditioning were part of the routine program for each patient.

TABLE I

DATA ON PATIENTS WITH GANGRENE TREATED BY SYMPATHECTOMY

Case No.	Sympathectomy, Months After Exposure	Extent of Gangrene: Part of Toes; No. Involved	Extent of Gangrene: Entire Toe; No. Involved	Extent of Gangrene: Metatarsal Heads Exposed; No. Involved	Amputation and Plastic Procedures	Effect of Sympathectomy on Neurologic Signs: Hypesthesia	Effect of Sympathectomy on Neurologic Signs: Hyperesthesia	Pain on Weight-Bearing After Operation
1	L-5		L-4	L-3*	AO; RA			Moderate
2	R-8	R-1			AC	Relieved		Slight
3	R-7	R-2			AO; RA; SG			Moderate
4	L-2	L-3			E			Slight
5	R-2; L-2.5	R-2; L-2	R-2; L-1	R-1; L-1	AO			Slight
6	R-1.5; L-2	R-1	R-3; L-3	R-1; L-1*	AO; TG			Slight
7	L-2	L-2			E	Relieved both feet		Slight
8	R-2	L-2	R-3	R-1*	AO; SG	Relieved		Moderate
9	R-2; L-2.5	R-4; L-4			E		Relieved	Moderate
10	R-2	R-2			E			Moderate
11	R-2; L-2	R-4; L-1	R-1	R-1*	AO; FG			Moderate
12	R-3	R-1	L-2	L-1*	AO; PG; SG	No change	No change	Moderate
13	R-2; L-2		R-5; L-5	R-4; L-2	AO; TG; SG			Slight
14	L-1; R-1.5	R-1	L-5; R-4		AO; SG	Relieved		Moderate
15	L-2.2	L-1			E	No change		Moderate
16	L-2	L-2	L-2		AO; SG	Relieved		Slight
17	R-2.2	R-2			E; AC; SG			Moderate
18	L-1.5	L-5; R-1			AO; SG			Slight
19	L-2.2	R-5			AO; SG			Moderate
20	L-2.2	R-2	L-5	L-4*	AO; TG; SG	Relieved		Moderate
21	R-2	R-5; L-3			AO			Moderate
22	L-2.3	L-1			E	Relieved		Moderate
23	R-2.5	R-5			E; AO	Improved		Slight
24	L-1	L-2			AO; SG			Slight
25	L-2.5; R-3.3	R-5; L-5			AO; SG; RA		No change	Moderate
26	R-1	R-1			E	No change		Moderate
27	L-1.2; R-1.7		R-5; L-5	R-3; L-3*†	AO; SG; TG	Relieved		Slight pain in ankle; none in foot
28	L-1.5	L-4; R-1			E; SG; AC			No pain
29	L-1.5	R-3; L-3			AO; SG; RA			Moderate
30	L-4	L-4			AO; SG; RA		No change	Slight

The symbols used in column 6 (Amputation and Plastic Procedures) are as follows: AO—Amputation without primary closure; AC—amputation with primary closure; RA—reamputation; PG—small deep grafts; SG—split-thickness graft; TG—tube-transfer graft; E—excision of gangrenous plaques.

* Portion of metatarsal heads removed.

† Portion of one metatarsal head removed.

The effect upon the healing of gangrenous ulcers through increasing the circulation by sympathectomy is illustrated in Case 1 (Table I). The patient had been admitted to the hospital with an infected granulating stump from which the first four toes had been amputated four months previously. After treating the infection, small deep grafts were applied, but these were not successful. Since the foot was cold, wet and cyanotic and little epithelization had occurred during all the months of hospitalization, it was decided to perform a sympathectomy. Within a few days after operation healing was complete. The stump was subsequently revised because the skin over the distal end of the foot was delicate and thin.

TABLE II

SYMPATHECTOMY IN PATIENTS WITH EXCESSIVE SYMPATHETIC ACTIVITY

Case No.	Date Exposure	Date, Sympathectomy, Side	Manifestations Before Operation: Finding in Ordinary Environment	Manifestations Before Operation: Result of Exposure to Cold	Effect of Sympathectomy
1	June '43	8/2/44 R	Coldness, cyanosis, hyperhidrosis; numbness rt. leg and both feet; recurrent ulcers rt. foot; conversion hysteria	Intense coldness and numbness	Foot warm, dry and of good color; no discomfort; ulcers healed
2	Feb. '44	4/3/44 R* 10/17/44 L	Coldness, hyperhidrosis and burning and tingling lt. foot on walking; healed stumps, rt. 2, 3, 4, 5 toes; healed gangrene lt. 5th toe	Coldness increased	Rt. sympathectomy had aided healing of gangrenous toes. After lt. sympathectomy foot warm, dry and without cold sensitivity or pain on weight-bearing
3	Dec. '43	10/25/44 L	Severe hyperhidrosis, especially lt. foot, with maceration of skin and secondary infection, coldness and cyanosis; slight pain on weight-bearing	Coldness and cyanosis increased	Foot warm, dry and of good color; skin lesions healed; on exposure to cold no pain in lt. foot but still present in rt.; pain on weight-bearing unchanged
4	Feb. '44	12/16/44 L 12/21/44 R	Coldness, cyanosis, marked hyperhidrosis; pain on weight-bearing	Pain in feet; increased coldness and cyanosis	Feet warm, dry and of good color; reduction in pain on exposure to cold; pain on weight-bearing unchanged
5	Nov. '43	1/13/45 L 1/27/45 R	Coldness, cyanosis and marked hyperhidrosis with maceration of skin and secondary infection; some edema; throbbing and burning pain on walking	Tingling pain, both feet	Feet warm, dry and of good color, throbbing pain gone; edema improved; burning; pain on walking unchanged
6	Dec. '43	1/5/45 R 2/1/45 L	Coldness, cyanosis and hyperhidrosis; throbbing rest pain; pain on weight-bearing; hypesthesia	Coldness, aching and throbbing increased	Feet warm, dry and of good color; cold sensitivity partially relieved; throbbing pain and hypesthesia gone; pain on weight-bearing unchanged
7	Dec. '43	1/29/45 R	Hyperhidrosis, coldness and cyanosis; mild pain on weight-bearing	Coldness increased	Foot warm and dry; pain on weight bearing unchanged
8	Nov. '44	3/23/45 L	Pain on weight-bearing; some edema; uncomfortable hypesthesia	Coldness and numbness	Cold sensitivity relieved, edema, pain and hypesthesia unchanged
9	Dec. '44	7/23/45 L 8/2/45 R	Coldness, cyanosis and hyperhidrosis; slight pain on walking; healed superficial gangrene	Marked coldness, aching, tingling and burning pain	Complete relief of coldness, hyperhidrosis and cold sensitivity; pain on weight-bearing little if any better

* Performed in hospital overseas and not analyzed in present series.

In addition to the case reports in Table I, Case 1 in Table IV had deep gangrene of the plantar surface of both great toes which healed readily following bilateral sympathectomy and excision of the gangrenous portions. Figures 1 to 4 illustrate feet with varying degrees of gangrene and the results following sympathectomy.

PATIENTS SUFFERING FROM EXCESSIVE SYMPATHETIC ACTIVITY

Thirteen sympathectomies were performed on nine patients who were suffering from symptoms resulting from the presence of excessive sympathetic activity. In four individuals (Cases 3, 4, 5 and 7, Table II), the operation was performed chiefly because of otherwise uncontrollable hyperhidrosis which caused considerable distress, kept the socks almost constantly wet, and in two was associated with definite maceration of the skin followed by local infection. All had evidence of epidermophytosis and also definite sensitivity to cold.

In the remaining five cases in this group, sympathectomy was undertaken primarily because of cold sensitivity. All of these individuals developed intense coldness of the feet during exposure to a low environmental temperature, associated in two cases with a distressing sense of numbness and in two others with pain, not otherwise present. Four of these patients also had rather marked hyperhidrosis. In addition, one of them had recurrent superficial ulcers of the foot.

Results.—Following operation every patient in the above group developed warm, dry feet which were much less responsive to cold. The associated discomfort was likewise minimized. In the case of two individuals with maceration of the skin and subsequent local infection, the infection cleared up shortly after sympathectomy. That the sympathectomized limb maintains greater warmth and has better arterial pulsations than the untreated extremity is demonstrated in Table III.

TABLE III

EFFECT OF SYMPATHECTOMY ON SKIN TEMPERATURE OF TOES AND ON OSCILLOMETRY AT ANKLE

Case No.	Oscillometry		Skin Temperature °C.*	
	Nonoperated Limb	Operated Limb	Nonoperated Limb	Operated Limb
1	1	2.5	23.5–25	35 –36
2	4.5	5.5	18 –19	33.5–35
3	2	4.5	21.5–23.5	28 –29
4	1.5	4	28 –29	32 –35
5	0.75	2.5	19 –22.5	31.5–34
6	4	5	25 –25.5	30 –31
7	3.5	5.5	24.5	32 –35.2
8	3	5	30 –32	33 –35.5
9	2.5	4	24 –29	34 –34.5
10	1.2	3	21	32
11	4.5	5	22.5–23.5	27.5–28.5
12	7	9	31	32 –33
13	2	4	24	34
14	2	5	27.5–28.5	36.5
15	0.75	4	27 –27.5	33.5–34.5
16	3	4	31 –31.5	34 –34.5
17	3	6.5	31.5–33	35.5
Average	2:6	4.6	25.8	33.2

* Readings indicate range of temperature in first, third and fifth toes.

PATIENTS SUFFERING FROM PAIN ON WEIGHT-BEARING

Fourteen sympathectomies were performed upon ten patients primarily because of pain in the foot on weight-bearing. This was present either in the metatarsal area or less frequently in the heel. In an attempt to minimize the symptoms, the patient would resort to applying the weight of his body to the nontender portions of the feet. As a result, he walked either on his heels or along the lateral edges of the feet. All of the individuals also showed evidence of fairly marked vasospasm.

TABLE IV

SYMPATHECTOMY IN PATIENTS WITH PAIN ON WEIGHT-BEARING

Case No.	Date Exposure	Date Sympathectomy and Side	Location of Pain	Type of Walking	Other Manifestations	Results
1	Dec. '43	6/12/44 L 6/19/44 R	Metatarsal area	Heel	Gangrene, both great toes; coldness, cyanosis and hyperhidrosis	Normal walking, without pain; gangrene healed; good color and warmth; no sweating
2	Dec. '43	7/21/44 R 8/18/44 L	Metatarsal area	Heel	Coldness, cyanosis and hyperhidrosis; marked edema after 7.5 months' bed rest; marked hyperesthesia	Pain on weight-bearing unchanged; good color and warmth; no sweating; edema gone; hyperesthesia gone except in distal fourth, both feet
3	Mar. '44	8/9/44 R	Metatarsal area	Heel	Coldness, cyanosis and hyperhidrosis	Pain on weight-bearing unchanged; good color and warmth; no sweating
4	Mar. '44	4/4/44 L* 8/18/44 R	Metatarsal area	Heel	Coldness, cyanosis and hyperhidrosis, rt. foot	Original operation made foot warm, dry and of good color and decreased edema. Second had no effect on pain on weight-bearing, made foot warm, dry and well-colored
5	Nov. '43	8/23/44 R	Metatarsal area	Heel	Coldness, cyanosis and hyperhidrosis	Pain on weight-bearing unchanged; good color and warmth; no sweating
6	May '43	8/30/44 R 9/11/44 L	Heels, ankles and rt. 1st metatarsal head area	Limp	Coldness, cyanosis and hyperhidrosis; slight edema	Complete relief of pain on weight-bearing and of vasospasm
7	Jan. '44	9/22/44 R	Metatarsal area and heel	Limp	Lt. peroneal and rt. tibial paralysis	Pain gone from heel but unchanged in metatarsal area
8	Nov. '43	1/5/45 R 2/12/45 L	Metatarsal area	Limp	Coldness, cyanosis and hyperhidrosis; marked pain on exposure to cold	Walking distance before onset of pain increased from ⅛ to over 1 to 2 miles; good color and warmth; no sweating; no cold sensitivity
9	May '43	2/1/45 L 2/13/45 R	Heels	Toes; lateral edge of foot	Coldness, some burning rest pain	Almost complete relief; no pain on standing or walking except after very long distances; rest pain almost completely gone; feet warm
10	Nov. '44	7/31/45 L	Lt. metatarsal	Heel	Gangrene, lt. great toe; coldness, cyanosis, hypesthesia, distal fourth, both soles	No pain in foot on weight-bearing; slight pain, lt. ankle, on prolonged walking; gangrene healed; foot warm and of good color; hypesthesia disappeared from both feet

* Performed in hospital overseas and not analyzed in present series.

FIG. 1.—Two patients with extensive deep gangrene. A-1, B-1 and B-2, condition originally. A-2, B-3 and B-4, final results following bilateral sympathectomy and amputation. Good functional foot obtained in both cases. Head of the first metatarsal left exposed after amputation in each instance and in Case B, a part of the metatarsal head had to be removed.

Result.—The results following sympathectomy in this group of patients were variable. In the two individuals (Cases 6 and 9, Table IV) in whom the symptoms were limited chiefly to the heels, complete relief in both feet followed the operation. Another patient (Case 7) had pain in one heel and in the meta-

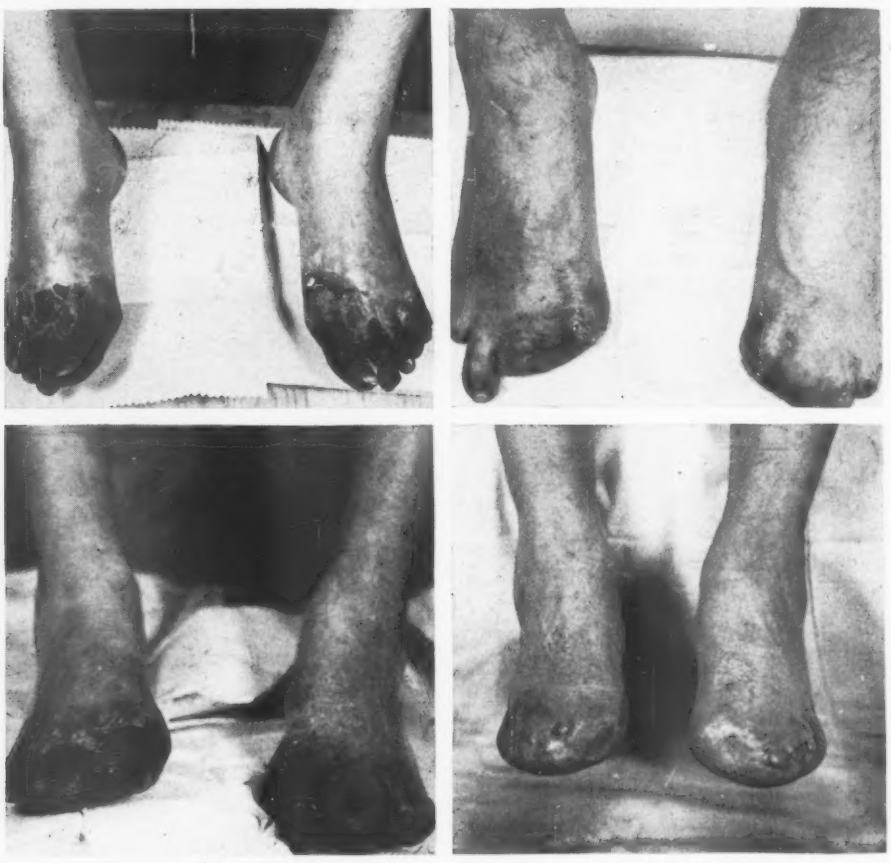

FIG. 2.—Two patients with extensive deep gangrene. A-1 and B-1, condition originally. A-2 and B-2, final results following bilateral sympathectomy and amputation. Satisfactory healing and good functional result obtained. Split-thickness grafts utilized in Case A to aid healing. Heads of both first metatarsals exposed following amputation in Case B, and a transfer-tube graft used to cover the defect of the right foot. The fourth and fifth toes stiff and painful and subsequently amputated.

tarsal area, and, again, relief occurred in the former site. Of the 11 sympathectomized limbs in which there had been pain primarily in the metatarsal area, complete relief occurred after operation in three (Cases 1 and 10), partial relief in two (Case 8), and no change in six (Cases 2, 3, 4, 5 and 7). One of the patients (Case 8) who showed some improvement could now walk one to two miles before pain appeared, whereas previously this distance was only one-eighth-mile, or less.

FIG. 3.—Patient with extensive deep gangrene. (A) Condition on admission. (B) After bilateral sympathectomy and amputation. (C and D) The final result. First and third heads of metatarsals on left and the first four on right exposed after amputation. A tube-transfer graft used to cover defect of right foot. A good functional result obtained.

Besides the information obtained from the above group of patients, additional data on the effect of sympathectomy upon the symptoms associated with weight-bearing were collected from the other two groups. Of those cases tabulated in Table II, one individual (Case 2) had burning and stinging pain in the left foot on walking, which disappeared following operation, while in seven, no change was observed postoperatively. Of the three patients listed in Table I who were ambulatory on admission, the discomfort on walking was improved after sympathectomy in one, while in the other two no change was noted. When the remaining 27 patients in the group began to walk again,

FIG. 4.—Patient with extensive gangrene. (A and B) Condition after bilateral sympathectomy and amputation. (C and D) The final result. Transfer-tube grafts necessary to cover defect of both feet. The first three metatarsal heads exposed on both feet, and part of the right first metatarsal head removed. A small sequestrum delayed complete healing. Good functional result obtained.

after healing of the lesions had occurred, two experienced no pain in the feet with weight-bearing in the sympathectomized extremities, while nine had slight, and 16 moderate complaints.

PATIENTS WITH NEUROLOGIC AND OTHER DISTURBANCES

In many of the patients in the above three groups, different types of sensory

disturbances were present. These were affected in a variable manner by sympathectomy. In some instances no conclusions could be drawn because of inadequate notes concerning neurologic signs following operation. In those individuals in whom pertinent data were available, hypesthesia was completely relieved in 11 extremities, improved in one, and unchanged in four. Hyperesthesia was relieved in one, improved in two, and unchanged in three. However, it must be stated that some patients, while undergoing no specific treatment, also showed definite improvement or relief of sensory disturbances. Furthermore, in two individuals hypesthesia disappeared from both feet following unilateral sympathectomy.

In a number of the patients in whom there was coincident slight edema of the feet, no significant alteration was noted following sympathectomy. However, in one in whom marked swelling had persisted for nearly eight months of complete bed rest (Case 2, Table IV), spectacular subsidence of the edema occurred within 48 hours after operation. Subsequently there was no recurrence except for slight swelling after prolonged standing or walking.

In practically all of the patients with extensive gangrene and in many of the others without loss of tissue, signs of osteoporosis were noted in the admission roentgenograms. Subsequent films, taken at intervals during the course of the hospitalization, showed no significant difference in bony changes in the sympathectomized as compared with the untreated extremities.

Discussion.—The data presented in this communication substantiate in part the view that in trench foot elimination of excessive sympathetic activity through sympathectomy has a beneficial effect on the course of the disease. It would appear that this operation has a definite place in the care of those patients who are suffering from deep gangrene. However, it must be pointed out that in this study no control series of cases was established and, hence, we have no unequivocal evidence in this regard. Certainly, in the case of superficial gangrene, healing occurs readily and without the benefit of sympathectomy. Nevertheless, it is our general impression that in those individuals with extensive gangrene, in whom there is obvious evidence of vasospasm, sympathectomy will play an important rôle in accelerating the rate of healing of the lesions and in preserving as much tissue as is possible.

Again, for those patients with marked cold sensitivity, associated with extreme hyperhidrosis, maceration of the skin and secondary infection, sympathectomy is a valuable therapeutic aid. In the case of the existence of cold sensitivity alone, the decision as to whether this operation is indicated should depend to some degree upon the type of life the patient is to lead and the climate in which he is to live. Certainly, it should not be considered in the light of a routine procedure in the treatment of this complaint.

Sympathectomy regularly eliminates the signs and symptoms of vasoconstriction and produces a warm, dry limb, of good color. However, it is not felt that vasoconstriction, *per se,* in the absence of annoying symptoms related to it, is sufficient reason to perform the operation. Whether by relieving excessive vasomotor tonus and maintaining almost maximal circulation to a foot, a

more rapid return of the tissues to normal will result can only be determined by follow-up studies. Up to the present, there are insufficient data upon which to base any definite conclusions on this point.

The results of sympathectomy in the treatment of pain on weight-bearing are not clear-cut enough to warrant extensive use of the procedure in this regard. It is of interest, however, that in every instance of pain in the heel, complete relief of symptoms resulted.

With respect to the sensory disturbances, it would seem that sympathectomy is of some benefit. Since these are only of minor importance and certainly are not incapacitating, the operation is not indicated in the treatment of them alone.

In the evaluation of the preliminary use of a procaine sympathetic block to determine the possible effect of removal of sympathetic tonus, our results have at times been misleading. This has been particularly true in an effort to determine whether or not sympathectomy would relieve the symptoms associated with weight-bearing. Several patients who apparently had complete or considerable relief in this regard immediately after procaine sympathetic block, subsequently showed no improvement following sympathectomy. The difference in response may be explained on the possibility that the first lumbar sympathetic ganglion was also anesthetized during the block, while at operation it was routinely left intact. Unfortunately, this matter was not investigated further by studying the effect of anesthetization of this ganglion postoperatively. It is also possible that the patient's desire to be rid of an incapacitating difficulty may have colored and exaggerated his interpretation of any apparent relief of symptoms during the period of the block. In this respect, it can be stated that every effort was made to avoid any promises or encouragement prior to this procedure.

Despite the above experience, we still feel that sympathetic blocks are of value in certain instances in determining the advisability of sympathectomy. For example, in every individual in whom this operation is being contemplated for the treatment of pain on weight-bearing or marked sensitivity to cold, the preliminary results with procaine block should be carefully studied. In all instances in which little or no relief occurs, it is quite likely that sympathectomy will also yield disappointing results. Naturally, preliminary blocks are not necessary in the case of hyperhidrosis, since sympathectomy always eliminates sweating. Furthermore, since improvement in the cutaneous circulation invariably follows permanent removal of vasomotor tonus in patients with trench foot, preliminary procaine blocks are likewise not essential in the case of extensive gangrene with vasospasm. If this information should be required, the response to inhibition of vasoconstrictor impulses can be assayed during spinal anesthesia, before operation is begun.

SUMMARY AND CONCLUSIONS

1. The effect of lumbar sympathectomy in the treatment of the sequelae of trench foot was studied in a series of 66 extremities.

2. It was felt that this procedure played a definite rôle in accelerating the rate of healing of the lesions in patients with extensive gangrene associated with vasospasm.

3. It was also of aid in treating the maceration of the skin and the complicating secondary infection which result in patients with prolonged marked hyperhidrosis.

4. The procedure reduced the severity of the symptoms in those patients suffering from cold sensitivity.

5. It produced variable results in the treatment of pain on weight-bearing, but had some therapeutic effect on the sensory disturbances.

6. It is concluded that sympathectomy has a definite but limited use in the treatment of certain selected cases of trench foot. In the majority of patients it appears to have no applicability as a therapeutic aid.

The authors wish to express their appreciation to Captains P. B. Olsson, R. B. Murray and H. A. Aronson, who helped in the treatment of the patients in this series.

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CONGENITAL DISLOCATION OF THE HIP

M. Beckett Howorth, M.D., D.Sc. (med.)
New York, N. Y.

FROM THE COLLEGE OF PHYSICIANS AND SURGEONS OF COLUMBIA UNIVERSITY, AND THE NEW YORK ORTHOPEDIC HOSPITAL, NEW YORK CITY, N. Y.

EMBRYOLOGY AND INFANT ANATOMY

The search for the cause of congenital dislocation of the hip is concerned with the development of the embryo and the fetus, and the best surgical treatment of the condition, whether manipulative or open, is dependent upon a thorough understanding of the anatomy of the infant hip. Textbooks of anatomy and embryology are notably brief and often vague on the anatomy of the infant and the embryology of the hip, while, aside from the work of Strayer,[1] medical literature and the personal communications of those familiar with the embryology of other portions of the body are of little assistance here. Because of these considerations a study of the hip joints of available fetuses has been made.

There were 15 specimens ranging in fetal age between ten weeks and full term. As no hip with congenital dislocation was found in this group or could be located in the laboratories or museums of the Columbia University Medical Center in New York, the study was confined to normal hips. The muscles surrounding the hip joint were dissected in detail in the larger specimens, and the capsule of the joint, the femur and the innominate bone were studied in all instances. Dissections were made from various approaches in order to study various portions of the joint without disturbing them. Slides were made of sections from several of the hips and studied microscopically, but as these observations are irrelevant they will not be included here. Roentgenograms were made of the innominate bone and articulated femur in several instances.

The youngest femur measured 2 cm. over-all, and was estimated to be ten weeks old. The muscles of the hip and thigh were not differentiated from each other or their tendons, and consisted of pale homogeneous tissue. The gross proportions and relations of the capsule, femoral head and acetabulum were similar to those of the fetus at term and to the adult hip joint. The femoral head was smoothly rounded and hemispherical and fitted snugly into the well-formed acetabulum, where it was firmly held by a well-developed capsule. The femoral head and the acetabulum consisted entirely of cartilage, and measured 2 mm. in diameter. The femoral shaft was ossified through a length of 7 mm., and the iliac wing contained an ossification center 2.5 mm. across. The anteversion or anterior torsion (the angle between the longitudinal axis of the femoral head and neck and the transverse axis of the femoral condyles) was 15 degrees. The angle between the axis of the head and neck and the longitudinal axis of the shaft averaged 140 degrees. The motions of the joint, except extension which was moderately limited, closely approximated

those of the hips of young children. Thus, the hip joint may be considered perfectly formed in the embryo of ten weeks.

Seven hips of fetuses in the third, fourth, fifth and six months of life were seen, the femur varying in length between 3.3 and 8 cm. (Fig. 1 A, B). The muscles of these specimens were differentiated from each other almost completely and were easily identified, although they did not yet appear grossly to consist of muscle tissue and were poorly differentiated from their tendons. The blood vessels and nerves were easily distinguished. The gross proportions and relations of the structures at the hip were similar to those at term. The femoral head and the acetabulum consisted entirely of cartilage but ossification of the iliac wing had progressed to occupy one-half to two-thirds of its area and a large ossification center had formed in the ischium. There was a cartilaginous lip along the posterosuperior half of the margin of the acetabulum, comparable to the bony lip of the adult, and the labrum glendoidale had formed. The femoral head varied in diameter between 0.4 and 1.4 cm. The femoral shaft was still slightly flexible. The ligamentum teres was well formed but could be torn with little force. The anteversion of the femoral neck was 20 to 25 degrees, and the inclination of the neck to the shaft 120 to 140 degrees. The motions of the joint were complete except extension, which was limited to about 145 degrees by the twisting of the capsule. The fibers of the capsule were seen to run parallel to the neck with the hip flexed to 90 degrees, and, upon extension, to tighten by torsion, resulting in this limitation.

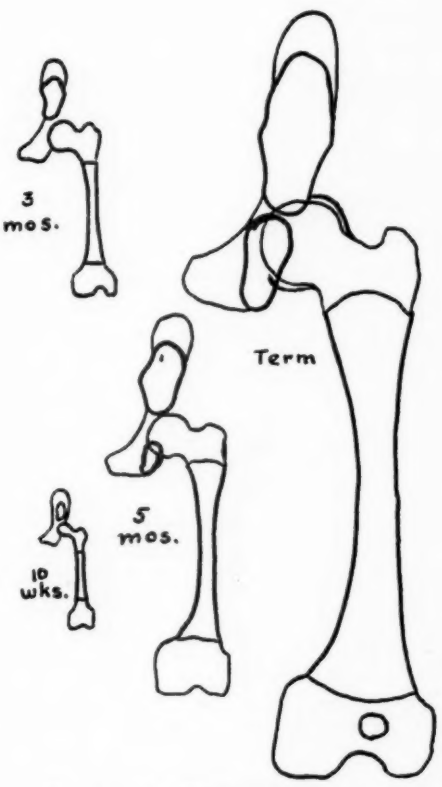


FIG. 1.—(A) Fetal specimens (½ actual size) at ten weeks, three months, five months, and term, showing size and shape of femur and innominate bone, with amount of ossification. Gross appearance similar to adult. Femoral head and neck and acetabulum are well-formed in cartilage, capsule and ligamentum teres well-developed.

Eight hips of fetuses in the seventh and ninth months were examined, the femora varying between 9 and 10.5 cm. in length. (Fig. 1 A, B.) The muscles were well differentiated and their tendons could be distinguished. Blood vessels and nerves were well developed. The ossified portion of the innominate bones occupied about five-sixths of the mass of each, but the acetabulum and femoral head were entirely cartilaginous. The anterior-inferior quadrant of the aceta-

bulum was shallow and the cartilage thin. The labrum glenoidale and the acetabular rim were well developed. The femoral head was 1.6 to 2.0 cm. in diameter. The ligamentum teres was 5 mm. in cross section and, in one instance, traction of several pounds was applied and a plug of cartilage to which it was attached pulled out of the femoral head but the ligament did not rupture. The Haversian gland was well developed. Anteversion varied between 20 and 40 degrees, and the inclination of the neck on the shaft was 110 to 120 degrees. Extension was limited to 160 degrees. The limitation of exten-

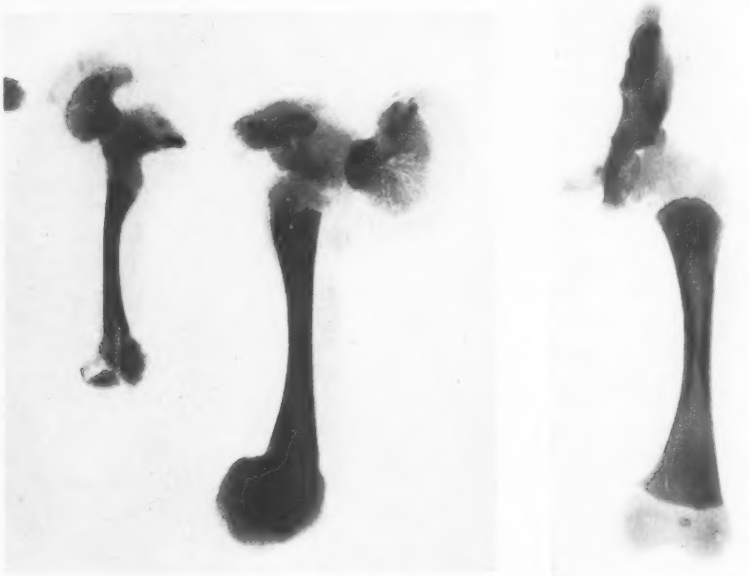


FIG. 1.—(B) Roentgenograms of fetal specimen at three months and at five months (actual size) and at term (reduced ½).

sion by the twisting of the capsule is considered to represent a phase in the evolution of the joint. (Fig. 2 A, B.) Young infants are found to have flexion deformities of the hips, gradually disappearing as the infants begin to stand. The hips of an infant of one year were studied also, but there were no additional findings of consequence.

The cause of congenital dislocation of the hip was not determined from this study. It was hoped that a clue could be obtained as to whether or not these dislocations are due to an hereditary defect, to a local metabolic disturbance or to the application of some force to the femur from uterine pressure or malposition *in utero,* but no defective hip was found, and no conclusion can be drawn here. It is likely that if the deformity is intrinsic to the development of the embryo it occurs in the anlage of the hip, as the joint is so well formed at and beyond the tenth week. There were differences in the male and female pelves of this group, comparable to those of adults, but none which would account for the great preponderance of congenital dislocation in female infants.

Should the deformity be the effect of the application of an abnormal leverage to the femur *in utero* it would appear that associated bowing of the flexible femur might follow such a force, but deformities of the femur are not found in

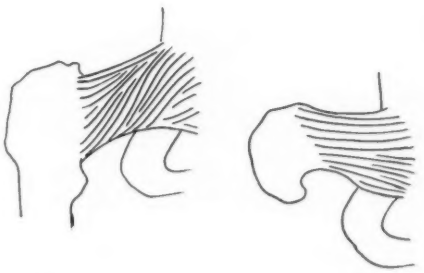
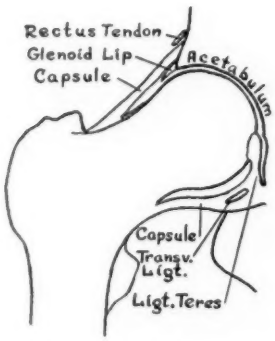


FIG. 2-A 2-B

FIG. 2.—(A) Hip joint capsule showing spiral twist of fibers in extension (from Spalteholz).

(B) These fibers are not twisted in the position of midflexion, but run nearly parallel with the neck.



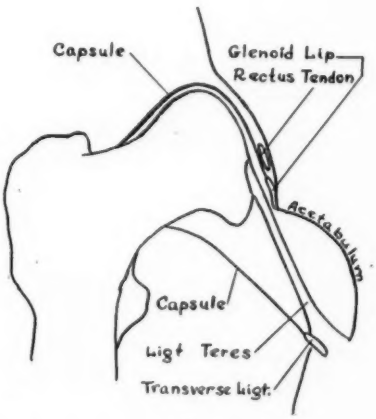


FIG. 3 FIG. 4

FIG. 3.—Normal hip, showing rectus tendon, capsule, labrum glenoidale, ligamentum teres, and transverse ligament.

FIG. 4.—Dislocated hip, showing outward and upward displacement of femur against ilium above acetabulum. Capsule and ligamentum teres elongated, capsule and transverse ligament pulled up over inferior portion of acetabulum. Labrum glenoidale and rectus tendon folded up against ilium. Acetabulum shallow, roof oblique, superior lateral margin defective. Femoral head flattened medially, protuberant inferiorly. Anteversion often present.

children with dislocated hips. No evidence has been found at birth or from operations upon young infants to support the possibility of dislocation by sudden trauma. It has been learned, through a personal communication from a research worker at the Rockefeller Institute, that congenital dislocation of

the hip occurs in rabbits, is apparently hereditary, and may be inbred. We have no evidence that the condition occurs in other animals, but an extensive search was not made.

Dislocation could be due primarily to a relaxed capsule or to a deformity of the acetabulum. At operation, the capsule has always been found elongated, necessarily, but the acetabulum is frequently too well formed to justify the supposition that it is the only primary factor. The ligamentum teres is not normally taut in the ordinary positions, so its relaxation could not be the cause of congenital dislocation. It does not appear that anteversion of the femur is the cause of dislocation, and it certainly is not the sole cause, as many dislocated hips have been found without abnormal anteversion. The position of flexion, external rotation and adduction would favor dislocation, and anteversion would increase this tendency. It appears that the inception of the deformity probably occurs in early embryonic life, and it is likely that relaxation of the capsule is the primary factor. It is desirable that hips younger than the tenth week be carefully studied and that a thorough search be made by pathologists, obstetricians and gynecologists for dislocations of the hip in fetal specimens in order that the cause of this condition may be determined.

There are special anatomic considerations related to these early specimens which are of great importance in the treatment of congenital dislocation of the hip. The greatest relaxation of the capsule is in the midflexed position; thus, the opening into the acetabulum should be largest with the hip flexed, and with a constricted capsule reduction should be more likely in some flexion than in extension. (Fig. 2 A, B.) Furthermore, the immobilization of the hip in forced extension and internal rotation is likely to result in a temporary ischemia by the torsion of the capsule and may be followed by coxa plana. When the acetabulum is too small to receive the whole femoral head it is desirable to enlarge it; in the infant there is a thick mass of cartilage in the superior acetabulum, a moderate portion of which can be removed with a gouge without exposing the ossified portion of the bones, but in the older child bone would be exposed at a depth of about one-eighth inch. The cartilage of the inferior acetabulum is thin and incomplete in the infant; thus, gouging of this area would probably result in opening into the upper thigh or the pelvis. Finally, because the acetabulum is cartilaginous it is difficult in the stabilization operation to construct a bony shelf which would be low enough to really support the hip.

PATHOLOGY

More than 100 hips have been examined at operation by the author, he being the responsible surgeon for 60 of the hips. The operative records of 85 additional hips have been reviewed. These studies form the basis for the following observations:

The femoral head in almost all instances was dislocated outward, upward, and forward, the capsule and rectus tendon being elongated to follow the head (Figs. 3, 4, 5 and 6). The capsule was usually somewhat thickened. The

muscles, tendons and fasciae attached to the trochanters and their neighborhood, and the innominate bone, were elongated or contracted to fit the altered mechanical situation. Abduction was limited by the leverage of the femur against the ilium, with the adductor muscles resisting. The posterior dislocations were few and almost uniformly occurred in older children.

It seems likely that the posterior dislocation is simply the ultimate result of the primary anterosuperior dislocations in which the capsule becomes greatly elongated, allowing the head to rise upward and swing backward on the ilium, since it is limited anteriorly by the tendons attached to the spines of the ilium. The greater proportion of posterior dislocations reported by others may be due to the greater percentage of older cases. It is probable that a posterior dislocation is more likely to occur in the absence of marked anteversion, which throws the head forward, and this is borne out by the fact that anteversion in these posterior dislocations was usually absent, whereas there was often a retroversion.

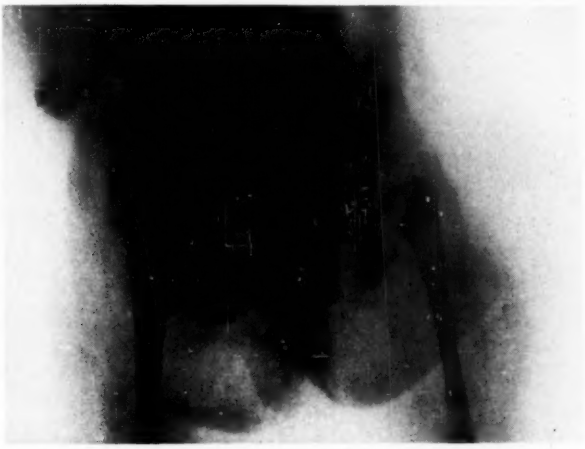


FIG. 5.—Roentgenogram of bilateral dislocation in specimen at 8th fetal month, showing clearly the lateral and upward displacement of the femur.

Telescoping (instability on pushing up and pulling down the leg) was present in varying degree, being less marked in the anterior dislocations and often as much as one inch in the posterior ones (Figs. 4 and 6). There was rarely appreciable relaxation on pulling the femur laterally or backward and forward in the anterior dislocations, but such relaxation was usually present with a posterior dislocation, being sometimes as much as one-half inch. Several of the hips were not completely dislocated, a portion of the femoral head remaining under the superior lip of the acetabulum, the head sliding in and out on manipulation.

The principal obstructions to bringing the femoral head down to the level of the acetabulum, which is necessary for the accomplishment of reduction, were the adherence of the capsule to the ilium above the acetabulum and the

contraction of fasciae and muscle sheaths (Fig. 4). While the capsule was not always pulled up enough to result in adherence to the ilium, in the remaining cases the cartilaginous superior margin of the acetabulum, the labrum glenoidale and the rectus tendon were turned upward and deformed in such a way as to produce the same effect. The adductor longus and gracilis are the muscles which most commonly interfere with traction, the rectus femoris, sartorius,

FIG. 6-A

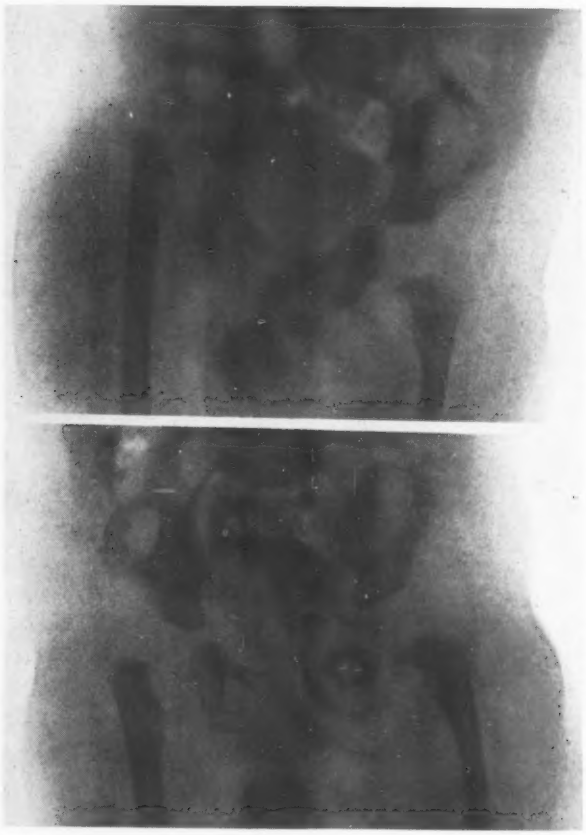


FIG. 6-B

FIG. 6.—Roentgenogram of dislocated right hip as shown by displacement of femur laterally and upward. Telescoping, as shown by:
(A) Upward pressure—further displacement upward.
(B) Traction—femur down to nearly normal level in relation to acetabulum, in position for reduction.

tensor fascia femoris, iliopsoas, and gluteals being frequently contracted also. The fascia lata, particularly the iliotibial band, often offers strong resistance. The remaining adductors and the hamstrings rarely offer difficulty.

It was possible in many of the younger cases to bring the femoral head down to the level of the acetabulum by traction or flexion. In many such

instances an attempt was made to reduce the dislocation at open operation just before opening the capsule. It was found impossible in about half of these hips to accomplish the reduction, whereas about half of those reduced were found to redislocate easily upon bringing the thigh from the abducted position toward neutral. Upon opening the capsules the reasons for this difficulty were obvious.

The inferior portion of capsule was nearly always pulled up over the lower portion of the acetabulum and, in the children who had passed infancy, had become firmly attached to the margins of the acetabulum (Fig. 4). There was often also a slight side to side constriction of the capsule but in all hips up to

FIG. 6-C

FIG. 6.—(C) Result at age seven years, following failure of closed reduction at two months, successful open reduction at one year.

the age of six years, and in many of the older ones, the superior portion of the acetabulum was open and the superior portion of the capsule pulled upward away from the acetabulum. Thus, the deformity in the capsule is not a typical hour-glass contracture as so often described in the literature. Usually the transverse ligament of the acetabulum was pulled up with the capsule and hypertrophied, more effectively blocking the acetabular opening. Adhesions between the two synovial surfaces were rarely found. The Haversian gland, located in the acetabular fossa, hypertrophies in response to the absence of the pressure of the head. This hypertrophied gland was usually found to fill the inferior third of the socket. In some instances this tissue filled the whole acetabulum and gradually grew into and replaced the acetabular cartilage. In such hips the acetabulum was sometimes found to be obliterated by a mass of fibrous tissue. The ligamentum teres was elongated directly in proportion to the amount of dislocation. Often it maintained its usual diameters or became thickened, but in other hips it was greatly attenuated, split longitudinally, frayed, ruptured or absent. Some of the instances of ruptured or absent teres ligaments might have been due to the traumatism of closed manipulations, but

such conditions have been found in hips which were never manipulated. One or both stumps were usually found, except in the patients older than ten years. Occasionally the ligamentum teres presented evidence of recent injury. It usually oozed blood slightly from its proximal stump when divided at operation, but was only once seen to bleed enough to suggest that it was furnishing an important portion of the blood supply to the head.

The acetabulum was usually well formed in these infants, although in many hips the superior cartilaginous margin had been pushed up or even folded back upon the ilium, resulting in an oblique defective socket for the femoral head and a poor false acetabulum at the acetabular margin. Fig. 4. It appeared that the plastic cartilage had been molded by the pressure of the femoral head. If the capsule was sufficiently relaxed to permit complete dislocation upward on the ilium, the acetabular margin often escaped this deformity. In such cases the capsule was sometimes adherent to the ilium and cartilaginous in this area, forming a false acetabulum; in others the capsule was loose and movable and the femoral head had no fixed support. The depth of the acetabulum was not great enough to accommodate the head in about half of the hips, and in a smaller proportion the diameter of the head was greater than that of the acetabulum, whereupon the head could not be forced into it. These abnormalities were more frequent and more severe in older patients, the superior lip usually being absent.

The femoral head was frequently flattened medially; this was more common in the hips in which the head was impinging against the superior margin of the acetabulum. Near the junction of the head and neck inferiorly there was usually an enlargement of the bone, which was apparently due to the medial flattening of the head and probably associated with some circulatory disturbance. This elevation was frequently large enough to give the inferior half of the head a shape somewhat similar to that of a door knob. The femoral head and neck were often broadened. Occasionally there was some irregularity of the surface of the head in the older subjects.

TREATMENT

The ideal treatment of congenital dislocation of the hip is to secure the earliest possible reduction with the least possible traumatism, and with immobilization just long enough to result in permanent maintenance of the reduction. Such treatment should involve the least risk to the life of the patient from the anesthetic and from shock, and a minimal risk of infection. Simple open or closed reduction with immobilization would be insufficient to maintain the reduction of some hips because of the deformity of the femoral head or the acetabulum or the relaxation of the capsule, whereupon it is often necessary to correct these abnormalities to secure a good result. In other cases it is impossible to reduce the dislocation without unreasonable traumatism or division of tissues, followed by stiffness or weakness. The best alternative in such cases is the construction of a bony support for the femoral head in the dislocated position. The following statements in regard to treatment are based upon a

study of more than 100 closed and about 200 open operations and 50 shelf-stabilization operations, including follow-up examinations one or more years after operation, with particular reference to pain, fatigue, disability, limp, limitation of motion, telescoping and roentgenographic appearance.

It was found that forceful manipulations, even if successful in reducing the dislocations, often resulted in stiff hips and occasionally were complicated by such accidents as a fracture of the femoral neck. Subsequent open operations usually demonstrated that manipulative reduction was obviously impossible in most of the hips which were not reduced by manipulation (about 50 per cent). One-third of the dislocations which were apparently reduced recurred partially or completely. Accordingly, open operations gradually replaced closed operations in the older children, as they could be done with equal safety to the child, with less traumatism and with a greater chance of initial and final success. Obstructions to reduction, faulty acetabula and relaxed capsules could be corrected at open operation.

CLOSED REDUCTION

A closed reduction is the operation of choice in infants younger than one year. The hip can often be reduced under anesthesia by the simple maneuver of Hibbs: Flexion to 90 degrees, followed by abduction and extension, with manual lifting of the greater trochanter forward and sufficient internal rotation to counterbalance the anteversion present. It is unnecessary to use even the mechanical table with gentle leverage which Hibbs devised for the purpose, while such traumatizing procedures as that of Lorenz should be definitely avoided. Sometimes reduction can be accomplished by simple traction, internal rotation and abduction, but this is not the most favorable method as the capsule is twisted and narrowed upon extension. The hip should be immobilized after reduction in a plaster-of-paris spica in moderate abduction, and enough internal rotation to compensate for the anteversion, but the position should not be forced as the tension on the capsule may cause a circulatory disturbance which may result in coxa plana. The reduction should be verified by a roentgenogram; it is desirable to have the axis of the femoral head and neck directed toward or just below the center of the acetabulum. If a careful first attempt fails it is rarely possible to reduce the hip at subsequent attempts. The immobilization should be maintained for three to six months, varying with the stability of reduction. The child may be allowed to walk within two months of reduction. Weight-bearing is an aid to the proper molding of the joint surfaces if there is no tendency to subluxation.

There is a fair chance of success with a closed manipulation in children between one and three years old. Accordingly, at this age a single gentle manipulation may be attempted first when it is not obvious that such a procedure would be hopeless. The chance of failure with manipulation becomes progressively greater with increasing age after three years, so that in the hands of a surgeon familiar with the open operation it is undesirable to subject the child to a procedure which offers little probability of success except in an

occasional carefully selected case. However, when the surgeon is not familiar with the open operation, and it is not available in his locality, a closed manipulation is warranted at any age when there is a possibility of success. Adductor longus and gracilis tenotomies at the groin are often necessary in the older children and are far superior to the brutal methods of tearing these muscles, popularized by some of the earlier workers. Preliminary traction with adhesive tape or a Kirschner wire with such an apparatus as that of Thornton or the Taylor hip splint is often desirable, but it will usually require several weeks to secure a stretching which will permit reduction without great tension. Roentgenograms taken during traction will indicate the probability of bringing the head down to the level of the acetabulum (Fig. 6 A, B). The roentgenogram at this age will also demonstrate the obliquity of the acetabular roof, and a comparison of views taken standing and under traction will show the amount of relaxation of the capsule but will offer no clue to the width of the opening into the acetabulum.

OPEN REDUCTION

Open reduction of the hip should be attempted (in capable hands) after the age of one year whenever closed reduction fails, and should be the operation of choice in children past three years except in unusual instances. Open reduction should rarely be attempted in infants younger than one year because of the immaturity of the acetabulum, the additional operative risks of the anesthetic and infection by fecal contamination, and possible feeding complications. Operation should not, however, be delayed after this time because the deforming effect of weight-bearing begins to act as soon as the child begins to stand, months before he can walk alone. Reduction may be obviously impossible in children past eight years because of the absence of a socket or the extent of the dislocation as indicated by the standing and traction roentgenograms, but the possibility of reduction is often indeterminate at this age period and can only be decided at operation. As a shelf-stabilization operation is usually a desirable alternative, operation is justifiable even when reduction appears unlikely. Preliminary skeletal traction may be used if the femoral head remains high above the acetabulum in the roentgenogram made under traction.

The hip-joint is approached through the Smith-Petersen incision, care being taken to avoid injury to the vessels and nerves passing across the thigh just below the femoral neck, and the capsule is freed from the gluteus minimus above and the iliopsoas below. The capsule is incised anteriorly close to and parallel with the acetabulum and the joint explored. All procedures are performed with the utmost gentleness. Frequently the entrance to the acetabulum is not more than one-half of an inch in diameter and reduction is impossible without enlarging the opening. This is done by incising the capsule and transverse ligament inferiorly across the constriction. The capsule should never be cut superiorly, as its support may be lost and the cartilaginous lip of the acetabulum and the labrum glenoidale damaged. The femoral head may now be brought into the acetabulum by traction, abduction and internal rotation

or by the maneuver used in closed reduction. Usually it is found that the head cannot be entirely reduced because of the large mass of the redundant ligamentum teres and the enlarged haversian gland. The structures are therefore usually excised. The acetabulum may still be too small to hold the femoral head. The acetabular roof may then be enlarged and rounded by gouging the cartilage if it is sufficiently thick to allow this without exposing bone. When it has been necessary to gouge a new socket out of bone the hip almost always has become moderately stiff. Possibly this outcome could be avoided if the new socket were made sufficiently large and lined with fascia and the reduction maintained without tension, but this has not been done. Hey-Groves and Colonna report good results with freeing of the entire capsule medially and inserting it with the head into the acetabulum. The results with the shelf-operation have been so much better, particularly in the bilateral cases, than those in which a large area of bone was exposed in the acetabulum that the former is preferred. Occasionally the overgrowth of the cartilage of the head inferiorly is so great that reduction is obstructed. Some of this mass of cartilage may be trimmed away without stiffness resulting if bone is not exposed.

The capsule should be freed from the ilium superiorly when it is adherent. The rectus tendon, labrum glenoidale and superior cartilaginous lip of the acetabulum should be freed when they are everted, and allowed to come down to their normal levels. It is often impossible to bring the femoral head down to the level of the acetabulum without dividing some of the extrinsic resisting structures. An adductor tenotomy should be done first. It may be necessary to lengthen the rectus and sartorius tendons and the iliotibial band. The use of skids or forceful maneuvers for reduction is undesirable and unnecessary if the capsule and contracted structures have been properly released, or if preliminary traction is used. If it appears that the hip could not be reduced after lengthening these structures the possibility of reduction without great danger to nerves and the circulation of the joint and the extremity, and subsequent stiffness, is not sufficient to justify further procedures, particularly in view of the lack of such disability in older patients who have had no treatment whatever, and the favorable results of the shelf-operation.

When reduction is secured it is desirable to insure its maintenance. Frequently a large pocket remains in the capsule into which the head can easily redislocate, and usually the capsule will not contract sufficiently to obliterate this pocket. The relaxation is generally greater anterosuperiorly, due to the dislocation of the head in this direction. A crescent of this portion of the capsule is excised, large enough to correct the relaxation but not large enough to impair external rotation (Figs. 7 and 8).

The amount of anteversion and its effect are determined at operation. The hip is adducted with upward pressure with the knee forward, and again with the knee in sufficient internal rotation to correct the anteversion, and the angle of redislocation noted. If the femur dislocates as the abduction is reduced before reaching a neutral lateral position with the knee forward but remains

socketed to at least 20 degrees of adduction in internal rotation, it will usually be desirable to correct the anteversion. This is done three to six weeks after reduction by a transverse supracondylar osteotomy, the upper fragment being

7-A

7-B

7-C

FIG. 7

FIG. 7.—(A) Subluxation left hip; closed reduction failed; open reduction at age nine months.

(B) Same hip at age two years. Acetabulum oblique, head displaced upward in acetabulum and slightly laterally. Degenerative changes in head due to circulatory disturbance (coxa plana).

(C) Same hip at age six. Acetabulum deep and round, coxa plana healed.

maintained in internal rotation by a steel pin driven through the femur below the greater trochanter and incorporated in the plaster. A Kirschner wire may be passed through the femoral condyles for control of the lower fragment (Figs.

9 A, B, C). The anteversion need rarely be corrected unless it is greater than 45 degrees.

The hip is immobilized in a plaster of paris spica from midthorax to toes, including the opposite thigh if it is advisable to fully immobilize the pelvis. The hip should not be held under tension in plaster, so that coxa plana may be avoided. The spica may be removed in six weeks if the reduction is very stable, but usually is left on for two months, rarely longer. When there is a probability

FIG. 8.—Dislocation left hip at age nine following open reduction at age seven, with osteotomy for anteversion. Acetabulum elongated and very shallow; head deformed, and dislocated opposite upper margin of acetabulum; coxa valga. A shelf operation should have been done.

of stiffness the plaster may be bivalved from the foot to the groin three or four weeks after operation and daily motion begun. The child is not allowed to walk at once upon removal of the spica but is kept in bed for one to four weeks, and massage and motion begun. Roentgenograms are made with traction and with upward push to demonstrate possible instability. When pain and spasm are absent, motion is fair or good, and there is no telescoping, walking is begun, first with crutches, then without support. The principles of treatment at this stage are to begin mobilization at the earliest safe moment and to delay weight-bearing until the extremity has recovered sufficient function.

SHELF STABILIZATION

It is usually impossible to secure a stable reduction with good motion in a congenital dislocation of the hip after the age of ten years. Some of the hips at this age are stable and symptomless in the dislocated position. Others are

painful and weak, moderate telescoping is demonstrated in standing and traction roentgenograms, and oblique views of the hip reveal the absence of any bony support. Sometimes in younger hips reduction is not obtained, or with the femur reduced the socket is so poor that the hip cannot be made stable by the methods previously described. In these types of cases it is desirable to support the hip by a bony shelf built above it to prevent instability and further dislocation. The hip may be pulled down by preliminary traction but it is

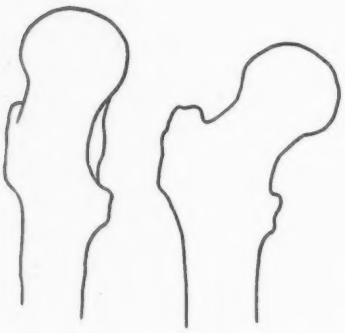


FIG. 9-A & B

FIG. 9-C

FIG. 9.—Anteversion:

(A) Marked anteversion, favoring dislocation.

(B) Normal hip.

(C) Operation for correction of anteversion: supracondylar osteotomy, upper fragment held in internal rotation by pin through femur at level of trochanters, position of lower fragment may be maintained by Kirschner wire through condyles (outside joint capsule), both incorporated in plaster spica.

undesirable to leave it under any tension after the shelf is made, as such pressure often results in partial absorption and irregularity of the femoral head. The shelf may be turned down from the ilium, the acetabular roof may be turned down and wedged as advocated by Gill, or a shelf may be driven into a slot above the acetabulum (Figs. 11 A, B, C). The first type of operation has usually proven most satisfactory, and will be described (Figs. 12 A, B).

The hip is exposed as at open reduction except that most of the iliac wing is exposed subperiosteally, care being taken posteriorly to avoid injury to the gluteal vessels and nerves, and usually it is unnecessary to free the capsule

FIG. 10

FIG. 10—(A) Dislocation right hip age two years; acetabulum shallow and oblique; marked anteversion.
(B) Same in internal rotation to show correction of anteversion.
(C) Same, three months after open reduction.
(D) Same, age four, two years after reduction. Slight subluxation. Coxa plana.

inferiorly. Taut structures are divided or lengthened to release tension, as in the open reduction, unless the capsule is very lax as in the high posterior dislocations where any further release would result in risk of the head slipping from underneath the shelf. The capsule is not opened unless reduction is to be attempted. Lateral and anteroposterior relaxation are tested to determine the width and length of shelf necessary. The shelf should be large enough to cover

10-E 10-F

10-G 10-H

(E) Same, age seven; further subluxation. Coxa plana healed.
(F) Same, age fourteen, further subluxation; acetabulum elongated and shallow. Head deformed.
(G) Shelf operation at age sixteen; iliac slab driven into slot above acetabulum.
(H) Same, one year after shelf operation. Relief of pain; improvement in gait and strength of hip.

the crest of the head in any position which it can assume. The proposed shelf is marked on the ilium in the form of a broad inverted U. A slab of bone, large enough to brace the shelf, is cut from the lateral cortex of the iliac wing anterosuperiorly and smaller reinforcing slabs and large chips are cut from the

remaining available portion of the ilium in such a manner as to weaken the ilium as little as possible. The shelf is freed with curved osteotomes to its base, usually three-sixteenths to one-quarter inch thick, and turned down over the capsule and femoral head, where it is blocked by a large slab wedged between the lateral margin of the shelf and the upper margin of its bed at an angle of about 45 degrees to the ilium. Reinforcing slabs and chips are inserted to fill the gaps, and particular care is taken to have the shelf perpendicular to the extended thigh. When the hip has been reduced or is merely subluxated the shelf includes a portion, if not all, of the false acetabulum and, occasionally, the

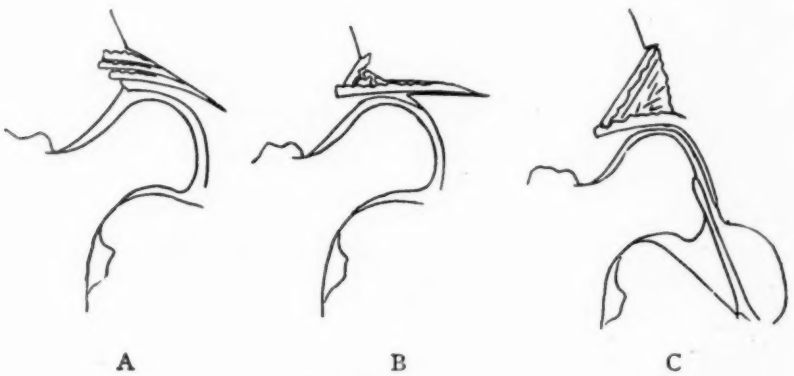


FIG. 11

FIG. 11.—Shelf stabilization operation:

(A) Hip reduced, roof of acetabulum turned down and wedged down by bone slabs cut from wing of ilium. For young children.

(B) Hip reduced, slab from iliac wing driven into slot at superior margin of acetabulum, and reinforced by block and chips above. For older children.

(C) Hip not reduced. Shelf turned down from wing of ilium and blocked there by slabs and chips from iliac wing. For older children and adults.

oblique portion of the acetabulum proper. The shelf does not become detached if handled carefully, additional support being furnished by the soft tissues at its base. Occasionally it is desirable to suture the slab to the shelf to prevent its slipping. The muscles are lifted forward over the shelf and carefully sutured to the tissues at the anterior inferior spine, the wound is sutured anatomically, as for open reduction, and a snug double spica applied to include the lower thorax and the foot of the affected side. The spica is worn for eight to ten weeks and weight-bearing begun two to four weeks later. The principles of postoperative treatment are similar to those for open reductions except that the solidity of the shelf for supporting the body weight must be determined roentgenographically.

ARTHROPLASTY, FUSION, AND OSTEOTOMY

Occasionally open or closed reduction results in a hip that is painful and somewhat stiff and deformed. The usual deformity is flexion, adduction and

internal rotation. There is little chance for improvement of these hips with exercises after two years from the time of reduction, and manipulation is likely to do more harm than good. Arthroplasty with the vitallium cup has rarely been tried in such hips under the age of ten years, but we have had one very good result in a child of five, and one fair result at the age of six, and good

A B

FIG. 12

FIG. 12.—(A) High dislocation of left hip with marked instability.
(B) Shelf turned down over head and reinforced with slabs and chips; one year after operation.

results in two adults. The cup was removed from the hip of the child of five after two years, and a well-formed head and acetabulum found. Arthroplasty is the operation of choice when both hips are affected, especially if both hips are stiff and deformed (Fig. 13). Hip fusion usually gives a better result if only one hip is affected, as there is no pain and the subject is able to stand, and even run, jump, dance and swim with the hip fused. We have performed only 13 hip fusions for congenital dislocation in the past 11 years, with almost uniformly good results. Both arthroplasty and fusion are difficult or impossible, however, if the hip is dislocated high on the ilium, as the iliac wing is so thin that there is not enough bone for either operation. A modified fusion may be done in such a case by using a tibial bone graft from the femur to the acetabulum or ischium through a subtrochanteric osteotomy. The Lorenz or the Schanz

osteotomy may be tried when both hips are dislocated high on the ilium, for relief of severe pain and instability.

CONCLUSIONS

The anatomy and development of the fetal hip from the tenth week to birth, the evolution of the anteversion and the torsion of the capsule, and the pathology of congenital dislocation of the hip as seen at operation from infancy to

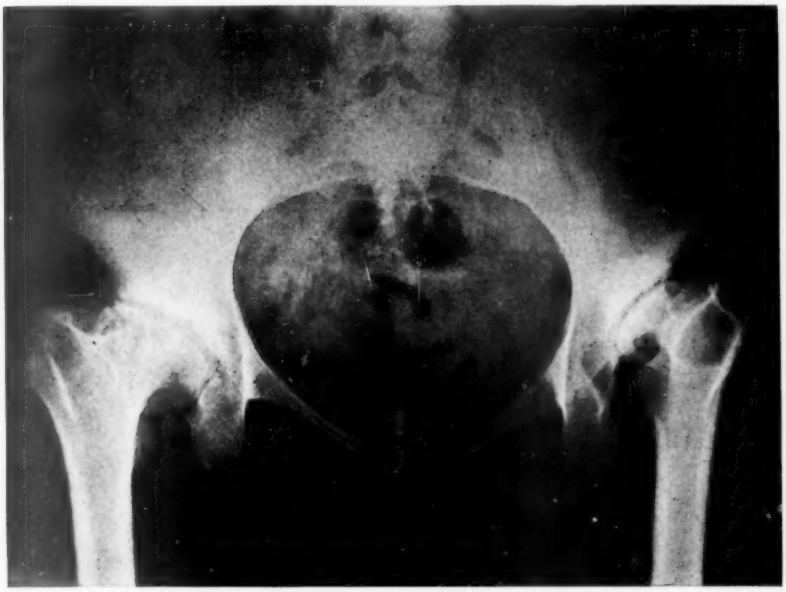


FIG. 13.—Bilateral congenital dislocation of hips, untreated, with marked deformity of femoral heads, necks, and acetabulums, and osteo-arthritis with cystic degeneration. Marked pain and disability. Suitable only for vitallium cup arthroplasty.

adult life are described. Congenital dislocations of the hip should be reduced as soon as possible after they are recognized, as the results are more favorable in proportion to the early age of the patient. Closed reduction is the treatment of choice for infants if it can be accomplished with little traumatism. Open reduction should be used for infants older than eight months if closed manipulations fail and for all older children when there is any possibility of securing a movable stable hip. Important anatomic points and variations in procedure, advisable for securing the best result in the individual case, are stressed. When open reduction fails or is inadvisable, the shelf-stabilization operation, or the vitallium cup arthroplasty should be used in selected cases, or an arthrodesis done. The results of the surgical treatment of congenital dislocation of the hip are very favorable when there is careful selection of type of treatment, due regard for operative technic and atraumatism, and proper after-care.

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AUTOGENOUS DICED CARTILAGE TRANSPLANTS TO BONE

AN EXPERIMENTAL STUDY

STUART D. GORDON, M.B., F.R.C.S.(C), M.S.(T), F.A.C.S.
AND
RUPERT F. WARREN, B.Sc., M.D.
TORONTO, CANADA

THIS INVESTIGATION was undertaken to study the histologic changes involved when diced autogenous rib cartilage was placed in a long bone defect. The immediate and late effects of such a transplant on shaft bone and the ultimate fate of the grafted tissues themselves were studied over a period of three months.

The literature on chondral grafts is extensive. It has been established that cartilage may be transplanted from one site to another in the same animal, and not only continue to survive but also to grow. Growth follows more readily if the new site is vascular. Cartilage may be grafted successfully from one animal to another of the same species and behave as an autogenous graft. This ability to survive homografting is shared by only one other tissue, namely, cornea. Cartilage is able to survive repeated transplantations and by successive regrafting will long outlive the normal lifespan of that particular animal. This tissue then possesses potential immortality. Survival in these cases is not due to regeneration from a viable perichondrium, as was once believed, but rather depends on the survival of individual chondrocytes themselves. (Dupertuis,[1] Loeb,[2-7] Bisgard[8]).

Many uses have been made of both living and dead cartilage in plastic surgery (Pierce,[9] Gillies,[10, 14] Peer,[11] Placio Posse,[12] Adler,[13] and others). One consistent objection to living cartilage grafts is their tendency to curl. Young[15] deposited small pieces of autogenous cartilage over the rectus fascia in dogs. He concluded, "autogenous rib cartilage finely chopped and seeded over the rectus fascia in a dog stays viable and fuses together into a solid sheet of opaque-like material." This fusion is by fibrous tissue. Grossly this mass has some of the properties of fibro-elastic cartilage. Peer[16] used this principle in humans and stored excess autogenous material in small pieces in the patients' soft tissues for later use in plastic repairs. He found the 'interdice' spaces filled with blood clot followed by an ingrowth of connective tissue and numerous blood vessels. "The smaller the graft, the better its chance of complete survival after transplantation." Practical use of diced cartilage has been made in restoring contours in plastic surgery (Young,[17] Peer[18]).

There has been a considerable amount of experimental work done on cartilage but to date no one has investigated the tissue changes that occur when diced cartilage is transplanted to a fresh bone defect. Previous studies have been directed to the reactions in soft tissues, where blood supply is adequate.

It has already been mentioned that survival and growth are known to result. But will cartilage continue to grow in bone? Is it replaced by bone and does it stimulate osteogenesis?

Material and Method.—Since early ossification in canine costal cartilage has been noted by other workers (Young[19]), and confirmed here, the rabbit was selected as the experimental animal of choice.

Under general anesthesia a small portion of the anterior ends of the lowest two ribs were obtained. Microscopic sections proved this to be true cartilage. The material was immediately diced into small cubes about 1 mm. in diameter. These were deposited in a long bone defect of a forelimb of the same animal. This defect was obtained by means of a small rongeur which removed the cortex over an area of approximately 0.6 cm. by 0.8 cm. When bleeding had ceased the defect thus created was tightly packed with the diced costal cartilage. The incisions were closed in the usual manner.

Animals were sacrificed at 24 hours, and thereafter at weekly intervals up to three months. In all, some 18 animals were studied. Sections were taken of the decalcified bone in the longitudinal axis of the limb so as to include the cartilage graft lying between normal shaft bone on either side of the transplant. Sections were studied after staining with hematoxylin and eosin.

OBSERVATIONS

Twenty-four hours after operation diced cartilage is seen lying within the bone defect, surrounded by blood clot, serum and narrow débris. No evidence of osteogenesis is yet visible.

One week later islets of living cartilage are surrounded by an ingrowth of connective tissue cells, blended with the perichondrium and running parallel to the dice surfaces. New cancellous bone trabeculae are seen within the medullary cavity on either side of the artificially repaired defect.

At the end of two weeks central portions of some dices have begun to show cystic changes, with flattened chondrocytes lying against one side of their enlarged lacunar wall. Towards the periphery of each dice, there is normal appearing matrix and cellular structure. Cancellous bone has continued to encroach around the dices and there is a distinct demarkation between perichondrium and the surrounding connective tissue cells.

In about two and one-half to three weeks it is evident that not only is the dice surviving but the matrix of new cancellous bone has become structurally continuous with the matrix of the cartilage. This is not a matter of new bone being laid down in an area where the dice has been absorbed, for in the majority of cases the dice surface is not exposed, nor are tongues of invasion seen. Rather, it seems as though new bone had been laid down on the surface of the dice and the matrices had been fused together. In the following ten weeks the cartilage graft becomes progressively smaller. Nowhere is there evidence of absorption. No giant cells are seen and no inroads or tongues of connective tissue cells, except in those areas where necrotic or degenerating cartilage is found. Central portions of dices are made up of degenerating tissue, the

lacunae empty or greatly enlarged, while the surface of the dice is made up of normal healthy cartilage with a tendency for the cells to line up parallel to the surface of the dice.

At the end of three months a few small islets of cartilage persist deeply embedded in bone but appearing healthy and having a mottled uneven line of demarkation where matrices of bone and cartilage meet.

DISCUSSION.—Cartilage survives when transplanted to bone as it does when placed in soft tissues. It is evident that some process of replacement by bone is present here, not seen when cartilage is grafted to nonosseous sites. Replacement is not accomplished after absorption as would be the case with a bone graft. Instead it seems to be a creeping replacement after the two matrices become continuous.

Cartilage cells more remote from nutrition tend to degenerate and the lacunae to enlarge. Tissue nearer the graft surfaces is not influenced to the same extent. This is reasonable in view of the strangling effect of new bone matrix surrounding the dice. The problem of finer dicing for better survival must have its limitations as each dice becomes isolated by new bone in three weeks.

When a bone defect is repaired by tightly packed cartilage there is the classical picture of repair following injury. Ham[20] states: "Pieces of dead bone, or even masses of powdered calcium salts, can be considered to possess the distinct ability to incite a foreign body type of response.

"On the other hand, calcium salts, dead bone or calcified cartilage also exert a second type of stimulus particularly towards osteogenic cells which tend to incite new bone formation." We believe that living autogenous cartilage dices incite this second stimulus also.

Replacement of cartilage by bone is logical. It conforms to the pattern of growth in the young animal and the repair of fractures in the injured. In the latter cartilage is often seen in callus formation. Accordingly, some may question the authenticity of small islets of cartilage persisting in older grafts, suggesting perhaps they are the products of reparative processes. The constancy of the occurrence, the uniformity of the histologic sequence points strongly to the grafted tissue as being responsible for such islets in most cases.

In lower animals considerable repair of a long bone defect is accomplished without any graft. The persistence of viable cartilage islets in the midst of such active growth of bone emphasizes again its remarkable powers of survival.

CONCLUSIONS

1. When diced autogenous costal cartilage is used to repair a long bone defect in the rabbit, it remains viable for three months.
2. Cartilage dices act as a framework for the deposition of bone in a defect.
3. Replacement of cartilage by bone is slow and is not always preceded by absorption but tends to follow a creeping replacement process with a continuity of the two matrices.

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EXPERIMENTAL CARCINOMA OF THE GALLBLADDER*

SUPPLEMENTARY DATA

N. N. PETROV, M.D., AND N. A. KROTKINA, M.D.
LENINGRAD, U.S.S.R.

THE EXPERIMENTAL PRODUCTION of carcinoma of the gallbladder in animals was demonstrated by our work, published in 1933.[1] However, the results have not been accepted in the literature on this subject, partly due to our presentation of incomplete data. For example, in a review of the present status of the question in 1940, Lam[2] stated:

"Petrov and Krotkina reported, in 1928, that they could not reproduce carcinoma of the gallbladder in the guinea-pig by the introduction of foreign bodies, but in 1933 they reported success. Nineteen guinea-pigs were used. Small glass tubes containing one microgram of radium were inserted into the gallbladders of 12 animals, and seven controls had empty glass tubes inserted. They were trying to confirm the work of Barlow,[3] who had presented evidence that cancer of the gallbladder was due to the radioactivity of gallstones. They reported that carcinoma developed in two animals in each group. Three of the animals were said to have had multiple metastases and died of cancer. The fourth was operated upon at the end of the experimental period, and a carcinoma of the common duct was found. However, these authors did not choose to publish photomicrographs of the tumor tissue, but submitted drawings instead. Hence, it can be stated that, at the present time, experimental proof that gallstones cause cancer is lacking."

For fuller review, it should be noted that our original experiment, published in 1928, was relatively short-term in character, and only four animals survived longer than 15 months. In the second investigation, published in 1933, the first malignant tumor was found 16.5 months following the experimental procedure. Furthermore, two animals of the second group had not only metastases but also complete destruction of the gallbladder by tumor; hemorrhages in the peritoneum of one animal and in the pleura of the other were also encountered. Photographs of both these animals were included in our article.[1]

Absence of photomicrographs was undoubtedly a deficiency, especially since other authors reporting positive results on carcinogenesis in the gallbladder following introduction of foreign bodies,[3, 4, 5] also, did not present evidence that was sufficiently objective. This defect regarding the work of Leitch[5] had been criticized by Creighton,[6] and Rouillard.[7] We, therefore, desire to supplement our original report at this time. The delay in the answer to Lam's[2] criticism was occasioned by war conditions in Leningrad during 1941–1944. We referred to our collection of material on the original experiments and made histologic sections, as far as was possible, under the difficult circumstances.

* The manuscript for this article was received and translated by the American Review of Soviet Medicine, in New York City, N. Y.

The most illustrative material of all our positive results is hereby presented in the new photomicrographs.

In addition, we present photomicrographs from one new experiment in which 11 guinea pigs survived 14 to 34 months following the introduction into the gallbladder of glass rods, measuring 12 x 2.5 mm. The rods were sterilized by heat. In one animal there was considerable thickening of the gallbladder wall (to 3 mm.) 14 months following the experimental procedure. Atypical

FIG. 1

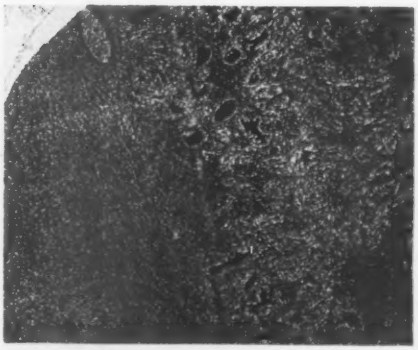
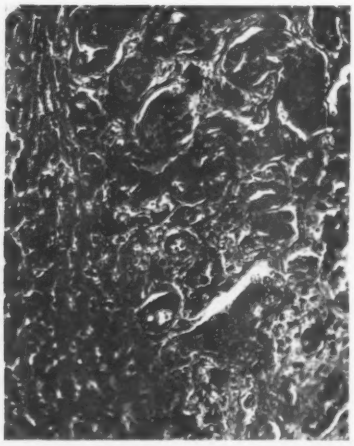


FIG. 2



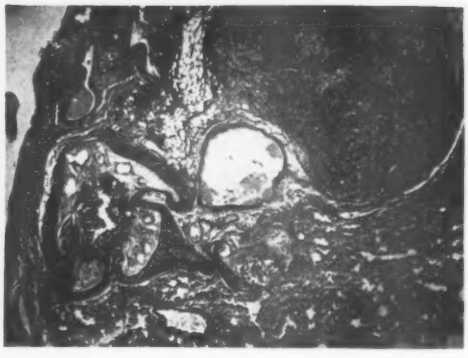


FIG. 3

FIG. 4

FIGS. 1–3.—No. 262: Growth of tumor in the liver. Low and higher magnifications.
FIG. 4.—No. 262: Metastasis in the lung.

epithelial cells, with hyperchromatic nuclei, grew in glandular patterns between muscle bundles of the gallbladder wall. A tumor mass, approximately 1 cm. in diameter, was found in the mediastinum between normal lungs. The mass was composed of glandular tissue similar to the original tumor, lying between fibrous connective tissue; in places the lumen contained amorphous material and leukocytes. This case was an early form of adenocarcinoma of the gallbladder, with metastasis to the mediastinum (Figs. 16–18).

In addition to the 11 guinea pigs mentioned above, we have three other

experiments, comprising 22 animals living from 15 to 40 months following the introduction of glass rods or tubes into the gallbladder. The animals did not develop malignant tumors, but, as in previous experiments, over half developed hyperplastic growth of the epithelium of the gallbladder.

In answer to doubts expressed up to the present concerning the production of malignant epithelial growth of the gallbladder by hard foreign bodies, *we present photomicrographs of all our positive observations.* Our experiments

FIG. 5 FIG. 6

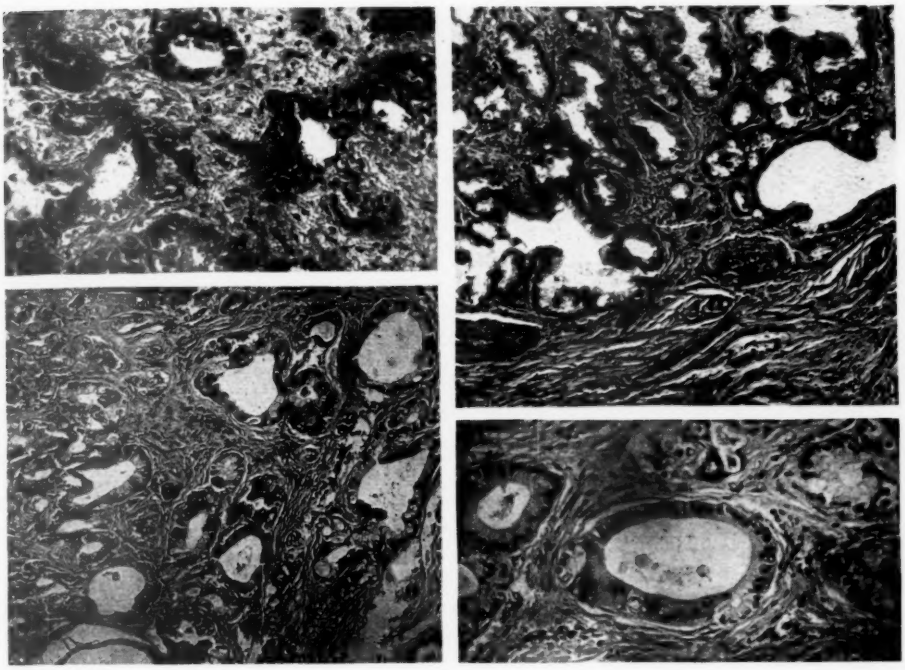


FIG. 7 FIG. 8

FIG. 5.—No. 262: Metastasis in the lung.
FIG. 6.—No. 267: Growth in the gallbladder wall.
FIGS. 7–8.—No. 267: Growth of tumor around common bile duct.

are summarized in Table I, which shows that five instances of malignant growth were obtained in 51 guinea-pigs following the introduction of hard foreign bodies into the gallbladder.

PROTOCOLS OF FIVE POSITIVE RESULTS

No. 262.—*Experiment 2:* Glass tube with radium. Tumor found 34.5 months after experimental procedure. Tumor penetrated diaphragm and destroyed the gallbladder. Metastases to lungs and omentum. The glass tube had disappeared. *Histologic Diagnosis:* Adenocarcinoma (Figs. 1–5).

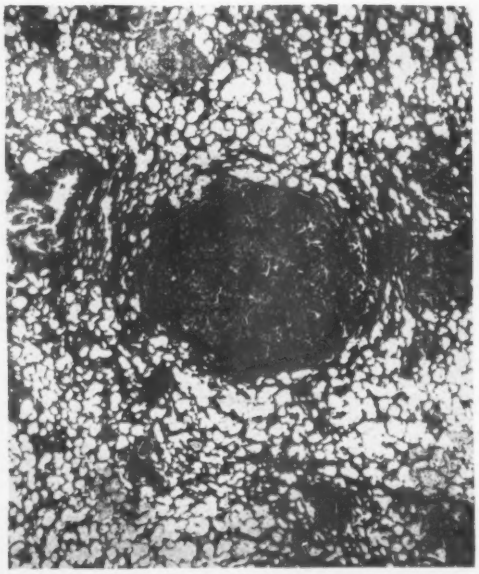
No. 267.—*Experiment 2:* Glass tube with radium. Tumor found 39.5 months after experimental procedure. Tumor around common bile duct, penetrating into the liver. The glass tube had disappeared. *Histologic Diagnosis:* Adenocarcinoma (Figs. 6–8).

No. 270.—*Experiment 3:* Sterile glass tube. Tumor found 16.5 months after experimental procedure. Gallbladder destroyed, tumor penetrated liver. Metastases to lungs, diaphragm and omentum. Hemorrhagic ascites. *Histologic Diagnosis:* Adenocarcinoma (Figs. 9–12).

No. 294.—*Experiment 3:* Sterile glass tube. Tumor found 31.5 months after experimental procedure. Metastases to lungs, diaphragm, and omentum. Hemorrhage in pleural cavities. *Histologic Diagnosis:* Adenocarcinoma (Figs. 13–15).

FIG. 9

FIG. 10



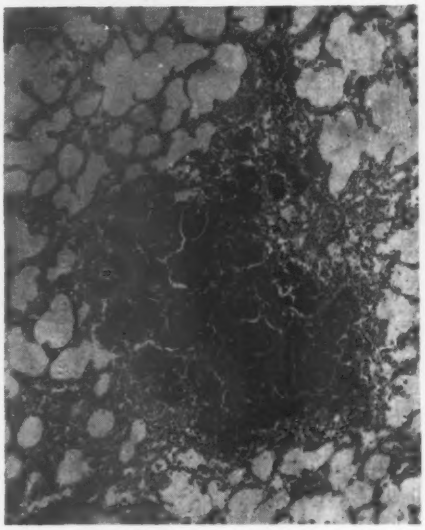


FIG. 11

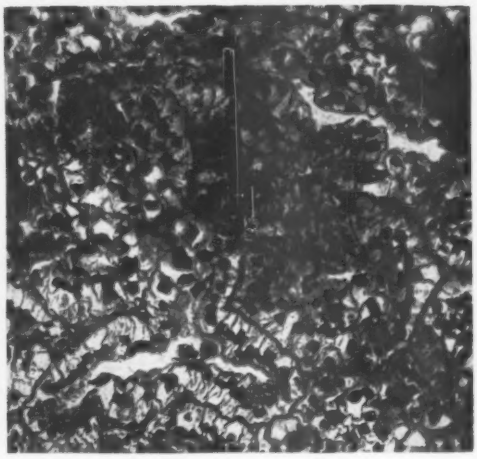


FIG. 12

FIG. 9.—No. 270: Growth of tumor in the liver.

FIGS. 10–12.—No. 270: Multiple metastases in lungs.

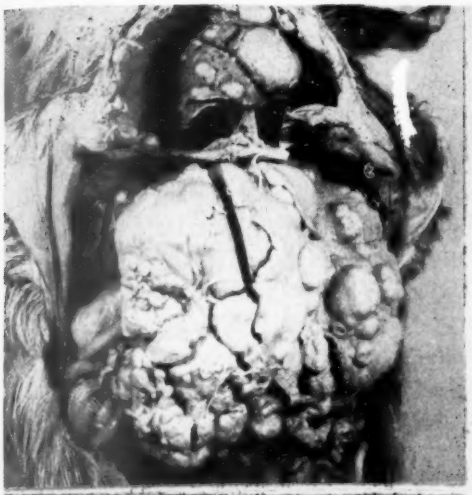


FIG. 13

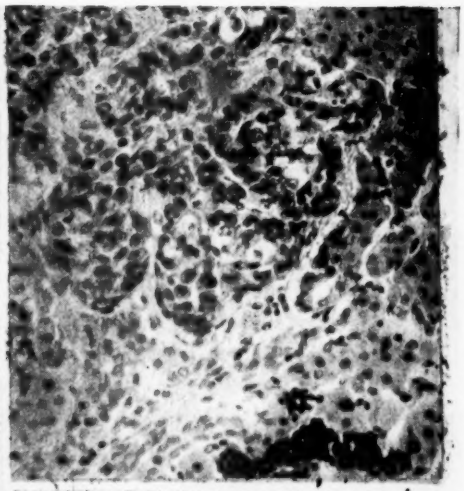


FIG. 14

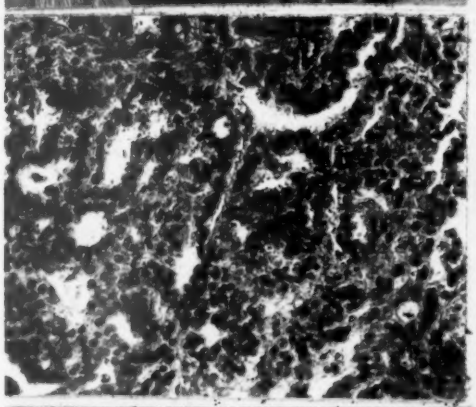


FIG. 15

FIG. 16

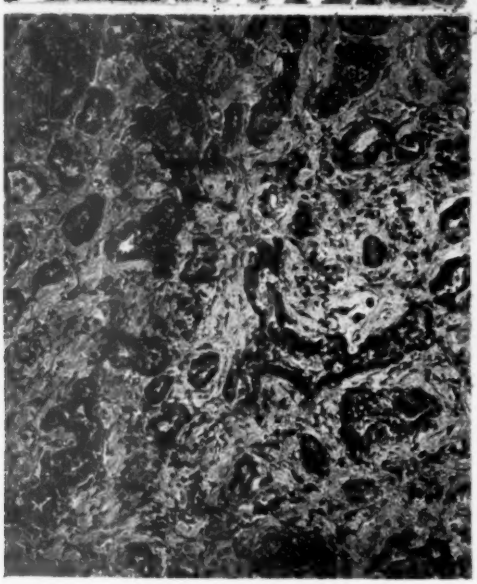


FIG. 17

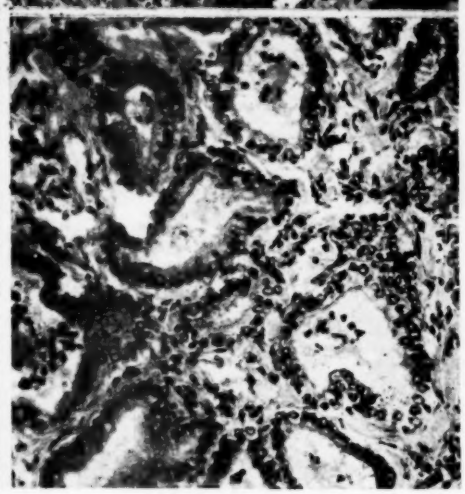


FIG. 18

FIG. 13.—No. 294: Gross appearance of animal at autopsy.
FIG. 14.—No. 294: Growth of tumor in the liver.
FIG. 15.—No. 294: Metastasis in the lung.
FIG. 16.—No. 678: Growth of tumor in the gallbladder wall.
FIGS. 17–18.—No. 678: Metastatic growth in the mediastinum.

No. 678.—*Experiment 5:* Sterile glass tube. Tumor found 14 months after experimental procedure. Hypertrophy of gallbladder wall, with atypical epithelial proliferations into muscle. Metastases to mediastinum. *Histologic Diagnosis:* Adenocarcinoma (Figs. 16–18).

The incidence of 10 per cent, if it is allowable to derive percentages from such small numbers, is higher than that noted in most statistics on the incidence of cancer of the gallbladder in human beings suffering from gallstones. Among 378 cases of cholelithiasis at the Obukhov hospital, in Leningrad, cancer of the gallbladder occurred in 15, or approximately 4 per cent. According to Lentze,[8] among 557 cases of cholelithiasis in women over 40 years of age, 5 per cent had cancer. Luelsdorf,[9] at necropsy, found cancer of the gallbladder in 56 of 892 cases of cholelithiasis, or 6.2 per cent. Graham[10] gave 8.2 per cent for the material at the Barnes hospital, and 10 per cent for the cases of Mayo-Robson.

TABLE I

INTRODUCTION OF FOREIGN BODIES INTO GALLBLADDERS OF GUINEA-PIGS

Exper. No.	Foreign Body	Number Operated Animals	Number Animals Surviving Over 14 Months	Number Animals With Epithelial Hyperplasia of Gallbladder	Number Animals With Malignant Tumors	Number Animals With Metastases
1	Gallstones.	17	4	12		
	Crude paraffin,	5		2		
	Saprol	4		3		
	Shale	2		2		
2	Glass tubes containing 1γ radium	12	8	9	2	1
3	Glass tubes, sterile, 10-16x2 mm.....	7	6	6	2	2
4	Glass tubes, sterile, 10-16x2 mm.....	17	9	1*		
5	Glass tubes, sterile, 10-16x2 mm.....	22	11	7	1	1
6	Glass tubes, sterile, 10-16x2 mm.....	8†	7	4		
7	Glass tubes, paraffined, and powdered with infusorial earth.....	6†	6	6		
	Total.....	100	51	52‡	5	4

* Histologic examination lacking in many cases.

† Animals of Experiment 6, and 2 animals of Experiment 7 received subcutaneously 400 mg. of o-aminoazotoluene during 3.5 months.

‡ Beginning at 2 months.

In statistics from various sources gathered by us in 1928, the occurrence of gallstones in primary cancer of the gallbladder in man is a general rule. Stones were found in 70 to 100 per cent of the total of 785 cases. On the other hand, Graham[10] found only three cases of cholelithiasis in 38 cases of secondary, or metastatic, carcinoma of the gallbladder.

It is concluded from these data that in the association of gallstones and cancer of the gallbladder, the rôle of the stones is primary. This furnishes special interest to the experimental attempts to produce cancer of the gallbladder following the introduction of hard foreign bodies into the viscus.

In regard to the experimental animals, it appears that the strictest requirements are met by guinea-pigs. According to Warren and Gates,[11] spontaneous cancer of the gallbladder has not been described in guinea-pigs.

Table I and the photomicrographs show that our results substantiate the possibility that sterile hard foreign bodies introduced into the gallbladder produce an hyperplastic growth of the epithelium in a large percentage of cases, and malignant epithelial proliferation, with local invasion and metastases, in a considerably smaller percentage.

The mechanism of this process is not evident. Most probably, the essential reaction consists of secondary degeneration and regeneration of the epithelium, caused by the foreign bodies. It is also possible to postulate a chemical carcinogenic effect in the stagnant bile and its products of decomposition. Factors of hereditary predisposition to cancerous growth also must play a rôle.

Another comment should be made, on the practically incurable nature of cancer of the gallbladder in man. Surgical removal is possible only in rare cases.[12] Radiation therapy is apparently entirely unsuccessful. Therefore, the only available method against this condition is prophylactic cholecystectomy in cholelithiasis, especially in women over 40 years of age. This conclusion was reached by Graham long ago, and he rightly stated that the danger of cancer of the gallbladder in such cases is greater than the operative risk in cholecystectomy when it is not complicated by jaundice.

SUMMARY AND CONCLUSIONS

Table I presents data on the introduction of sterile, hard, foreign bodies into the gallbladders of 100 guinea-pigs, of which 51 animals survived 14 months or longer. In five animals, after 14 to 39 months, there was found an epithelial proliferation of the gallbladder wall, with characteristics of malignant growth; local invasion in five, metastases to distant organs in four, and complete destruction of the gallbladder, with hemorrhage in serous cavities, in two. Photomicrographs of these observations are shown.

The development of malignant growth following the introduction of hard foreign bodies into the gallbladder is established. In guinea-pigs, the process requires over one and sometimes over two years.

The desirability of prophylactic cholecystectomy for gallstones in elderly women, as advocated by Graham, receives experimental support. The highly malignant course of cancer of the gallbladder, established by observations on man, is also confirmed by our experiments on guinea-pigs.

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ANNOUNCEMENT

UROLOGY AWARD

The American Urological Association offers an annual award "not to exceed $500" for an essay (or essays) on the result of some clinical or laboratory research in Urology. Competition shall be limited to urologists who have been in such specific practice for not more than five years and to residents in urology in recognized hospitals.

For full particulars write the Secretary, Dr. Thomas D. Moore, 899 Madison Avenue, Memphis, Tennessee. Essays must be in his hands before May 1, 1947.

The selected essay (or essays) will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Hotel Statler, Buffalo, New York, June 30-July 3, 1947.

Committee on Scientific Research,

MILEY B. WESSON, *Chairman*,
JUDSON B. GILBERT
ANSON L. CLARK

BRIEF COMMUNICATIONS

LARGE MELENA CAUSED BY SPONGE ULCERATING INTO LUMEN OF ILEUM MORE THAN TWENTY YEARS AFTER CELIOTOMY

HARRY C. SALTZSTEIN, M.D.
AND
JOHN O. RAO, M.D.
DETROIT, MICHIGAN

Case Report.—Catherine G., age 56, was admitted to the hospital in August, 1945, with a diagnosis of abdominal carcinoma. She had had a celiotomy for a pelvic complaint 25 years before, and an emergency celiotomy for bowel obstruction two and one-half years later. She had then been apparently well until 1939. In 1940, a diagnosis of duodenal ulcer was made and she was put on a diet. Occasional epigastric pain and eructations, with flatulence, experienced since that time, always responded to an ulcer regimen of diet, alkalies, *etc.*

On May 21, 1945, the patient was seized with a sudden attack of fainting, and passed a large amount of dark blood per rectum. She felt nauseated, seemed to taste blood, but never vomited. Frequent tarry stools occurred almost daily. Following four or five weeks of this, she was hospitalized at another institution. Their findings showed low blood pressure (95/60), some shock (which was remedied with blood transfusions), and a palpable movable mass, 3 x 4 inches in diameter, low and slightly to the left of the umbilicus. Roentgenograms of the stomach revealed no evidence of pathology. A barium enema filled the entire colon. The possibility of an extracolonic mass in the lower left abdomen was considered, although the small bowel was not roentgenographed. Discharged after a few days, she had another severe hemorrhage from the rectum within a week and was readmitted to the same hospital July 16, 1945. The stomach and duodenum were again roentgenographed, with negative findings. No source of bleeding was found. Chest roentgenographs and gastric analysis were suggested, and one consultant suggested celiotomy for suspected carcinoma, though this was not done.

The patient was transferred August 9, 1945, with the following diagnosis on the transfer chart: "Pelvic tumor with fixation to the bowel which causes the hemorrhage. May have to resect bowel."

When admitted, the patient was a very pale and bled-out woman, otherwise alert and active. Hemoglobin 3.5 Gm., or 21 per cent; R. B. C. 1,430,000. After repeated transfusions the hemoglobin finally went to 41 per cent (7.3 Gm.); R. B. C. 2,280,000. At times a mass could be felt in the left lower or midabdomen, but at other times it was absent. A barium enema stopped in the lower sigmoid. It was decided to explore the abdomen. *Clinical Diagnosis:* Far-advanced carcinoma of the sigmoid.

Exploration revealed a normal thin sigmoid colon, free and clear throughout. In the lower reaches of the ileum, there was a mass the size of a small orange which consisted of three matted loops of small bowel, plastered against a cyst-like, cheesy, inspissated mass. One loop of small bowel was easily detached, the second was so involved that the serosa along one side had been destroyed, and the third was intimately attached. There was an ulceration 1 cm. in diameter connecting the lumen of this loop of small bowel with the mass.

Upon further dissection, the mass was peeled away from the mesentery with a pseudocyst wall. It was not a dermoid, but, in the center was an old celiotomy sponge, still recognizable as such, in spite of an advanced stage of disintegration. Bleeding had been caused by the ulceration into the small bowel.

The ulcer was trimmed and closed, and the second loop, where the serosa was destroyed, was excised and reanastomosed. The patient made an uneventful recovery. Examination, January 12, 1946, disclosed her condition to be excellent, with no complaints, and bowel movements normal.

COMMENT.—Some 250 cases where a sponge had been left in the abdomen following a celiotomy were analyzed in 1940 by Crossen and Crossen. The clinical symptomology, as developed by them from this material, is briefly as follows: During the first month, the sponge is incidental to the inflammation and may suppurate and discharge through the incision or gravitate into the pelvis and rupture into the rectum with the abscess. After two or three months the acute inflammation subsides and the sponge, now a foreign body, may extrude, as such, through a sinus opening either externally or into the bowel, bladder or vagina.

When two or three years have passed, the sponge is well-encapsulated, and often exists harmlessly in the peritoneal cavity. After five years, the capsule becomes thin, and the mass seems like a dermoid or caseated node. Though it does not calcify, the sponge fibers resist disintegration and, even in very late stages, the sponge can be recognized as such.

Only 14 of these 250 cases were found five years or more, after the original operation. Four were found after 15 years.

Extrusion into the bowel lumen occurred in 28 per cent of the total cases, usually within the first ten months. The sponge was found entirely within the small bowel in about one-third of these. Symptoms of extrusion of the sponge into the bowel lumen were indigestion and obstruction; *i.e.*, mild pains at irregular intervals grading into violent colics, with vomiting. Emergency operations for intestinal obstruction had had to be performed. None of the case reports they reviewed showed gross blood or serious bleeding into the bowel lumen.

Harvey Stone reported 71 cases where many different sorts of intestinal lesions produced large melena of obscure origin, though in no instance was ulceration of an old celiotomy sponge into the intestinal canal listed as having caused severe gastro-intestinal hemorrhage.

However, very small lesions in the jejunum or ileum may cause severe intestinal bleeding. Segal and Merle Scott have recently called attention to this, and stress the fact that these cases mimic bleeding ulcer.

SUMMARY

A case is reported in which a sponge ulcerating into the ileum 25 years after celiotomy caused severe gastro-intestinal hemorrhage.

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PERFORATED CARCINOMA OF THE LARGE INTESTINE COMPLICATING PREGNANCY*

SUCCESSFUL OPERATIVE MANAGEMENT

W. B. SWARTLEY, M.D., Z. B. NEWTON, M.D., J. C. HARTMAN, M.D.
AND
J. W. STAYMAN, JR., M.D.
PHILADELPHIA, PA.

CARCINOMA of the large intestine during pregnancy requires the most careful surgical judgment in its management. The condition is a rare one, and each case demands especial evaluation because of the variable factors involved. However, in dealing with these cases certain underlying principles are to be kept in mind.

First, as Banner, *et al.,* stated in 1945, the question as to the best management for saving both mother and child must be answered. And if one of the pair has little, if any, chance of survival, how can the life of the other best be protected?

Second, the fact that pregnant women tolerate major surgical procedures as well as the nonpregnant has been brought out by Child and Douglas, in 1944, and reëmphasized by Finn and Lord, in 1945.

Third, the increased danger of peritonitis during pregnancy has long been known. In the series of Child and Douglas the maternal mortality rate was 66 per cent. The infant mortality is also increased, and labor is likely to be precipitated.

With these principles in mind, the approach to a given case of carcinoma of the large intestine during pregnancy is made less difficult. There is nearly unanimous agreement that in the early months of pregnancy the management of the malignancy should be the same as if the patient were not pregnant. Immediate termination of the pregnancy has been recommended by Adair, in 1940, on the basis that pregnancy increases the rate of growth of malignancy. However, there is not enough evidence to support the idea that pregnancy effects an extragenital malignancy to such an extent that it warrants termination.

In the latter months of pregnancy, with a viable fetus, the management is somewhat more difficult. Banner, *et al.,* seem to have the most logical approach to this problem. They recommend exploratory celiotomy to determine the operability of the lesion as soon as possible. If the lesion is inoperable and does not obstruct the birth canal, simple colostomy is done to permit normal delivery. If the lesion is operable, cesarean section, hysterectomy, followed by resection of the lesion is indicated. When the lesion is in the transverse colon and can be exteriorized, it may be possible to perform a stage-resection without entering the pelvis, thereby, permitting a normal delivery.

* Presented before the Philadelphia Academy of Surgery, May 6, 1946.

Unfortunately, pregnancy may mask the symptoms of carcinoma of the large intestine and the lesion may progress to obstruction or perforation before it is recognized. In these cases the management is most difficult. Berkeley, Bonney, and MacLeod, in 1938, outlined the management for cases with obstruction. They recommend hysterotomy, colostomy, and later resection, regardless of the stage of pregnancy. DerBrucke, in 1940, reported two cases of obstruction from carcinoma of the colon in pregnancy. He states that at that time a total of seven cases of obstruction of the colon from carcinoma were on record, and that only three of these cases were due to carcinoma of the colon:

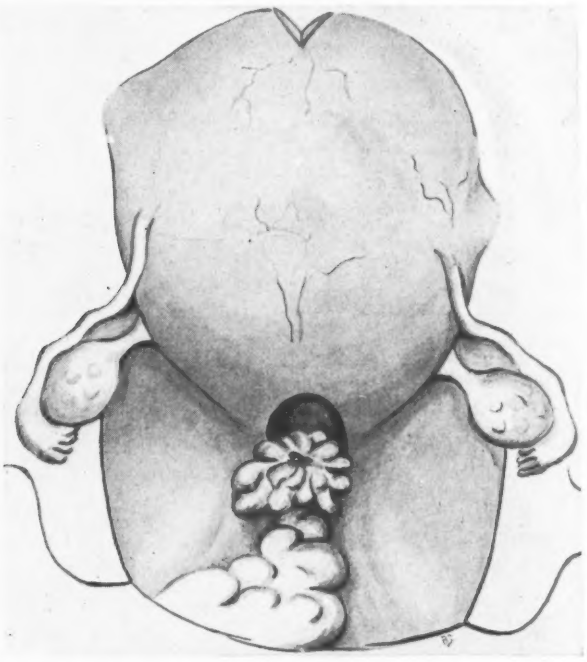

FIG. 1.—Diagram of pelvis at operation showing previously opened uterus containing fibroids, and carcinoma with perforation.

three were carcinoma of the ovary and one was carcinoma of the ileum. He recommends induction, with delivery from below, followed by celiotomy. Of the seven cases he reported the maternal mortality was 66 per cent and the infant mortality was 28 per cent. Finn and Lord, in 1945, reported the successful operative management of an obstructive carcinoma of the sigmoid colon in a six-month-pregnant woman. The tumor was removed by a three-stage procedure, and the patient subsequently had a normal delivery. They state that the pregnant uterus did not interfere significantly with the technical performance of the operation, and they support the statement of Child and Douglas: "Pregnant women tolerate even major surgical procedures quite as well as the nonpregnant."

There have been two previously reported cases of carcinoma of the large intestine with perforation complicating pregnancy. The first case was reported by Mengert, in 1933. His case was a thirty-year-old nine-month-pregnant woman who was admitted to the hospital because of cardiac decompensation. She developed symptoms and signs of peritonitis while in the hospital. A classical cesarean section followed by a subtotal hysterectomy was performed.

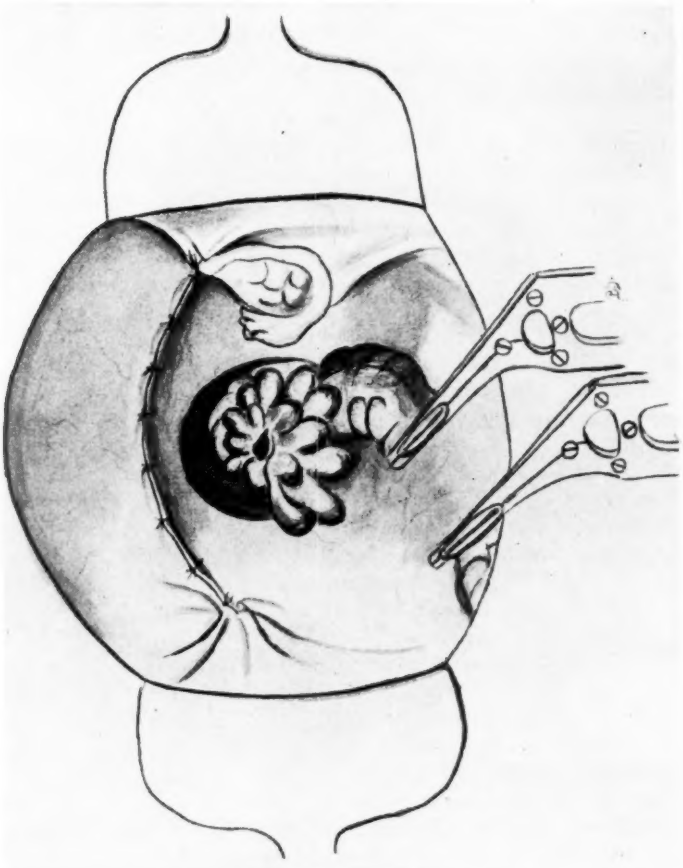

FIG. 2.—Diagram showing pelvis following the operative procedure.

The nature of the tumor could not be determined at operation and the abdomen was closed, with drainage. The patient died on the third postoperative day. Autopsy revealed an adenocarcinoma of the rectum, with death due to peritonitis. The second case was reported by Fournier, in 1937. This patient was a thirty-one-year-old quintipara, sextigravida who had a normal delivery. On the third day postpartem she began to have blood and mucus in her stools. She was given an enema, and shortly thereafter symptoms and signs of peritonitis developed. She was operated upon and a perforated lesion in the rectum was

found. A cecostomy was performed and the abdomen was drained. The patient died 12 hours later. Autopsy revealed a perforated carcinoma of the rectum.

According to Banner, *et al.*, there were 62 reported cases of carcinoma of the intestine complicating pregnancy up until 1943. They have added seven cases in 1945, Finn and Lord have reported one case, in 1945, and with the addition of this case the total number of reported cases is 71.

Case Report.—Mrs. C. T., a 39-year-old, white, primipara, was admitted to the Germantown Hospital Obstetrical Service, September 29, 1945, with the chief complaint of pregnancy, approximately seven and one-half months, associated with the sudden onset of lower abdominal, colicky pain, nausea and fever.

Her history dates back approximately two years, at which time she noticed increasing diarrhea and tenesmus. This condition progressed for one year, when she consulted a physician because of the appearance of blood and mucus in the stools and a weight loss from 128 to 113 pounds. She was told that she had "colitis" and was given medication. She was married shortly thereafter, and soon became pregnant. Following pregnancy the symptoms of "colitis" became more pronounced and she again consulted a physician in April of 1945. At this time the following studies were made: gastric analysis, stool examination, and barium enema. She states that she was given a sulfa drug and a nonresidue diet; and that she had no more progression of symptoms until the time of her admission. Her weight gain with pregnancy was 113 to 130 pounds; and her expectant date of delivery was November 10, 1945. There were no other significant facts in her history.

Physical examination was essentially negative except for the abdomen which revealed a nodular, pregnant uterus, seven to eight months, and bilateral lower abdominal tenderness. On rectal examination, a hard tumor mass could be palpated with the tip of the examining finger and there was considerable tenderness in the cul-de-sac. On admission, the temperature was 100° F; pulse 96; and respirations 20. Blood count: Hb. 85 per cent, R. B. C. 4,300,000; W. B. C. 23,400.

A surgical consultation was ordered, October 1, 1945, and the patient was proctoscoped. At the 10-cm. level a crater-like tumor was visualized which grossly appeared malignant. In view of the patient's acute symptoms and the proctoscopic findings, celiotomy was immediately decided upon.

Operation.—October 1, 1945: Under continuous spinal anesthesia, the abdomen was opened through a low midline incision, and a pregnant uterus containing several fibroids was encountered. A classical cesarean section was performed and a five and one-half-pound, living, male child was delivered. The liver was palpated and there was no evidence of metastatic growth. In the pelvis there was free pus, with marked inflammation and induration of the pelvic tissues (Fig. 1). There was a palpable tumor in the region of the rectosigmoid which was adherent to the surrounding tissues and contained a perforation. A subtotal hysterectomy, left salpingoopherectomy, and first-stage Lahey bowel resection were performed (Fig. 2). The abdomen was closed, with drainage in the pelvis. Operating time: one hour.

The patient withstood the operation well, and ran a normal postoperative course. She was given blood, fluids, sulfadiazine, and all necessary supportive therapy. She was discharged in good condition on the 32nd day. At home the patient improved. She gained weight and strength and her wounds healed satisfactorily.

She was readmitted one month later, December 3, 1945, and was immediately prepared for operation with blood transfusions and sulfathaladine. She was operated upon on December 5, 1945, under continuous spinal anesthesia. Exploration of the upper abdomen and liver again revealed no evidence of metastasis. In the pelvis the inflammatory reaction

had subsided considerably. The tumor in the rectosigmoid was present and was adherent to the surrounding tissues. An abdominoperineal resection was performed with considerable difficulty because of the adherent tumor. The patient withstood the operative procedure well.

The specimen consisted of sigmoid, rectum, and anus, with adjacent fat and enlarged lymph nodes. There was an annular carcinoma, with perforation in the region of the rectosigmoid junction. Microscopic examination of the specimen revealed adenocarcinoma (Fig. 3). There was no microscopic evidence of lymph node involvement in the mesentery.

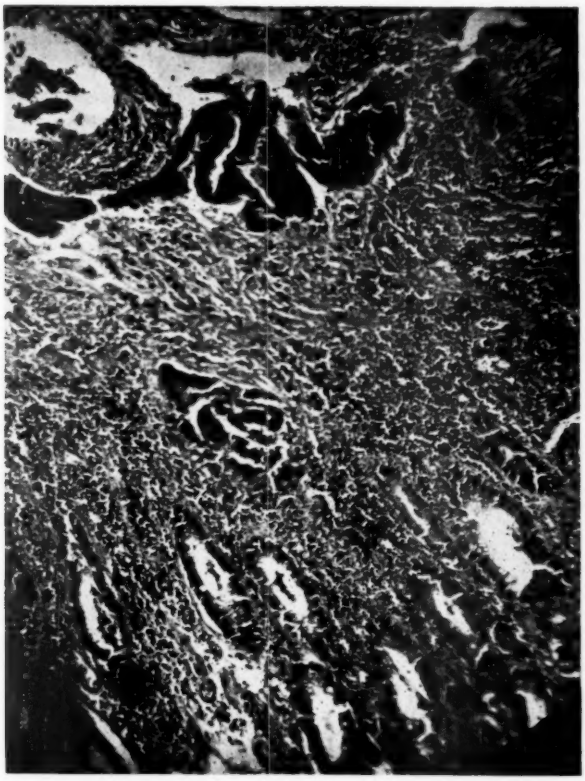

FIG. 3.—Photomicrograph of adenocarcinoma removed at operation.

The patient's postoperative course was favorable, and she was discharged on the 35th day. Since discharge the patient has gained weight and strength. Her wounds have healed well and her colostomy functions satisfactorily. Her weight on discharge was 88 pounds and is now 123. The child is likewise in good condition, weighing 20 pounds.

DISCUSSION.—We attribute the success in this case to the recognition of the principles mentioned earlier in this paper, modern pre- and postoperative care, chemotherapy, and the excellent coöperation between the Surgical and Obstetrical Departments.

This patient was in acute distress, and celiotomy was unquestionably indicated. With a viable fetus, cesarean section appeared to be the first logical

move. Had not cesarean section been performed we believe that this patient would have gone into labor as a result of peritonitis, and that both mother and child would have been subjected to a greater risk. Hysterectomy was carried out for the following reasons: to prevent infection of the open uterine sinuses in the presence of an already infected pelvis, to facilitate drainage of the pelvis, to allow greater exposure for the subsequent bowel resection, and to remove a uterus diseased with fibroids. The carcinoma was attacked in two stages because we feel that it would have been considerable added risk, and technically more difficult, to perform an abdominoperineal resection at the first operation. The prognosis in this case is to be guarded, as is the prognosis in all cases of perforated carcinoma of the large intestine. From a review of the literature, we find this to be the third case of perforated carcinoma of the large intestine complicating pregnancy, and the first case in which both mother and child have survived.

SUMMARY

1. The literature has been reviewed with respect to carcinoma of the large intestine complicating pregnancy.

2. A case of perforated carcinoma of the rectum complicating pregnancy is reported.

3. The principles of the management of such a case are outlined.

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Walter Estell Lee, M.D.
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